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PERIOPERATIVE MYOCARDIAL INFARCTION IN NON-CARDIAC SURGERY PATIENTS – CLINICAL PICTURE, PROGNOSIS, AND FUTURE IMPLICATIONS

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ACADEMIC DISSERTATION

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To my loved ones

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:

I Ollila A, Vikatmaa L, Virolainen J, Vikatmaa P, Leppäniemi A, Albäck A, Salmenperä M, Pettilä V. Perioperative myocardial infarction in non-cardiac surgery patients: A prospective observational study. *Scand J Surg* 2017; 106: 180-6..

II Ollila A, Virolainen J, Vanhatalo J, Vikatmaa P, Tikkanen I, Venermo M, Salmenperä M, Pettilä V, Vikatmaa L. Postoperative cardiac ischemia detection by continuous 12-lead electrocardiographic monitoring in vascular surgery patients: A prospective, observational study. *J Cardiothorac Vasc Anesth* 2017; 31: 950-6.

III Ollila A, Vikatmaa L, Virolainen J, Nisula S, Lakkisto P, Vikatmaa P, Tikkanen I, Venermo M, Pettilä V. The association of endothelial injury and systemic inflammation with perioperative myocardial infarction. *Ann Clin Biochem* 2019; 56: 674-83.

IV Ollila A, Vikatmaa L, Pettilä V, Wilkman E. Efficacy and safety of intravenous esmolol for cardiac protection in non-cardiac surgery. A systematic review and meta-analysis. *Ann Med* 2019; 51: 17-27

The publications are referred to in the text by their Roman numerals. These original publications are reproduced with the permission of their copyright holders

ABBREVIATIONS

A2RB	Angiotensin II receptor blocker
ACC	American College of Cardiology
ACEI	Angiotensin-converting enzyme inhibitor
ACP	American College of Physicians
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
aHR	Adjusted hazard ratio
AKI	Acute kidney injury
AMI	Acute myocardial infarction
ANP	Atrial natriuretic peptide
BMS	Bare-metal stent
BNP	B-type natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CAIS	Clinical anesthesia information system
CCB	Calcium channel blocker
CEA	Carotid endarterectomy
cECG	Continuous electrocardiographic monitoring
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine phosphokinase
CKD	Chronic kidney disease
CKG	Cardiokymography
CK-MB	Creatine kinase MB-isoenzyme
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CPR	Cardiopulmonary resuscitation
CPT	Current procedural terminology
CRI	Cardiac risk index
CRP	C-reactive protein
CS	Chondroitin sulfate
DES	Drug-eluting stent
DM	Diabetes mellitus
ECG	Electrocardiography

ECLIA	Electrochemiluminescence immunoassay
eCRF	Electronic case record form
EG	Endothelial glycocalyx
eNOS	Endothelial nitric oxide synthetase
ESA	European Society of Anaesthesiology
ESC	European Society of Cardiology
ESL	Endothelial surface layer
EVAR	Endovascular abdominal aortic aneurysm repair
FDM	Flow-mediated endothelium-dependent dilatation
GAG	Glycosaminoglycan
GMP	Guanosine monophosphate
HA	Hyaluronan
Hb	Hemoglobin concentration
HL	Hodges-Lehman estimator
HR	Heart rate
HS	Heparan sulfate
I-CAM	Intracellular adhesion molecule
ICU	Intensive care unit
IQR	Interquartile range
I/R	Ischemia – reperfusion
LAD	Left anterior descending coronary artery
LDL	Low-density lipoprotein
LEB	Lower extremity bypass
LOS	Length of stay
MET	Metabolic equivalent of task
MI	Myocardial infarction
MINS	Myocardial injury in non-cardiac surgery
NA	Not applicable
ND	Not defined
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NPV	Negative predictive value
NR	Not reported
Nrf2	Nuclear factor erythroid 2-related factor 2
NSQIP	National Surgical Quality Improvement Program
OAAA	Open abdominal aortic aneurysm repair

PACU	Postanesthesia care unit
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PMI	Perioperative myocardial infarction
pPCI	Primary percutaneous coronary interventions
PPV	Positive predictive value
PVC	Premature ventricular complex
RCRI	Revised Cardiac Risk Index
RIPC	Remote ischemic preconditioning
R-RCRI	Reconstructed Revised Cardiac Risk Index
RRS	Rapid response system
SAP	Stable angina pectoris
SD	Standard deviation
SE	Standard error
sTM	Soluble thrombomodulin
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient ischemic attack
TNF- α	Tumor necrosis factor alpha
TnI	Troponin I
TnT	Troponin T
tPA	Tissue plasminogen activator
TT	Thromboplastin time
UAP	Unstable angina pectoris
V-CAM	Vascular adhesion molecule
VSGNE	Vascular Study Group of New England

ABSTRACT

Objectives

Perioperative myocardial ischemia and infarction are frequent and serious complications, especially in elderly patients with cardiovascular risk factors who are undergoing major non-cardiac surgery. As the population in high-income countries is rapidly aging, the incidence and significance of perioperative cardiac complications will likely increase in the future. The objectives of this study were to determine the incidence and prognosis of perioperative myocardial infarction in patients undergoing non-cardiac surgery in a Finnish tertiary care hospital, to investigate the pathophysiology of this complication, and to review the current literature for preventive strategies.

Material and methods

Study I was a prospective observational study that investigated the incidence and 90-day mortality of perioperative myocardial infarction in 385 patients, aged 50 years or older, undergoing non-cardiac surgery in Meilahti Hospital. The performance of the Gupta cardiac risk calculator in non-American patient population was tested as well. Study II investigated the incidence of postoperative myocardial ischemia and its potential association with development of myocardial infarction. The prospective cohort included 51 high cardiac risk patients undergoing vascular surgery. The patients were postoperatively monitored with continuous electrocardiography and cumulative ischemic load was calculated. Study III aimed to further expand the current knowledge of the pathophysiology of perioperative myocardial infarction. The laboratory substudy included 75 patients from the first cohort and investigated the potential association of systemic inflammation and perioperative endothelial glycocalyx injury with development of perioperative myocardial infarction. Study IV was a systematic review and meta-analysis about the safety and efficacy of intravenous esmolol for perioperative cardiac protection. The review included 3 studies and 196 patients.

Results

The incidence of perioperative myocardial infarction was 7%, and it was associated with a fivefold increase in 90-day mortality. Gupta cardiac risk calculator performed fairly in predicting myocardial infarction. Postoperative ischemic electrocardiographic changes were common in high cardiac risk patients, with an incidence of 33%. Despite being mostly asymptomatic, cumulative ischemic load predicted perioperative myocardial infarction with an AUC of 0.87 (95% CI: 0.75-0.99). Systemic inflammation, reflected by elevated plasma interleukin-6 levels, was associated with perioperative troponin release and myocardial infarction. None of the measured endothelial glycocalyx injury markers (soluble thrombomodulin, syndecan-1, and vascular adhesion protein-1) was associated with perioperative myocardial infarction. Intravenous esmolol reduced the incidence of perioperative myocardial ischemia (RR =0.43, 95% CI: 0.21-0.88). No association with clinically significant bradycardia and hypotension could be confirmed. The studies included in the review were too few and too small to provide conclusive evidence regarding other clinically relevant outcomes, such as mortality.

Conclusions

Based on the data of the two prospective patient cohorts from a large Finnish tertiary care hospital, perioperative myocardial ischemia and infarction are frequent complications in surgical patients and are associated with poor prognosis. Without systematic perioperative ischemia monitoring, most of these complications remain undiagnosed. Future studies are needed to determine the pathophysiological mechanisms of perioperative myocardial ischemia and infarction, and to identify safe and efficient treatment strategies.

Keywords

Perioperative myocardial infarction, myocardial ischemia, non-cardiac surgery, cardiac troponin T, endothelial glycocalyx, prevention, esmolol

INTRODUCTION

Developments in surgical techniques, anesthesiology and perioperative care have improved postoperative outcome and survival of patients during the past decades. Thanks to the modern less invasive surgical techniques, elderly patients with several comorbidities can today be operated on to achieve more quality life years. However, major surgery may also precipitate to complications, perhaps the most underdiagnosed, yet potentially severe, of which are cardiovascular adverse events. Each year more than 10 million adults suffer a major cardiac complication in the first 30 postoperative days (Kristensen *et al.*, 2014; Botto *et al.*, 2014), and these complications account for at least one third of perioperative deaths (Botto et al. 2014; Kazaure *et al.* 2013; MacFalls *et al.*, 2008). Furthermore, perioperative cardiac complications carry a major economic impact, markedly increasing significantly the costs of medical care (Udeh *et al.*, 2014). As the Western population is rapidly ageing, it is likely that the incidence and relevance significance of perioperative cardiac complications will likely increase in the future.

Perioperative myocardial infarction (PMI) is the most severe perioperative cardiac complication, with a mortality rate of 20-40% (Devereaux *et al.*, 2005; Devereaux *et al.*, 2011; Davenport *et al.*, 2007; Ghaferi *et al.*, 2009). The observed incidence of PMI depends on the patient population, type of surgery, and perioperative surveillance method used. Large studies with prospective ischemia monitoring have shown incidence rates of 5-7% for PMI (Botto *et al.*, 2014; Devereaux *et al.* 2011; Devereaux *et al.*, 2008; Nagele *et al.*, 2013; van Waes *et al.*, 2013; Badner *et al.*, 1998). However, retrospective, register-based studies have reported incidences of less than 1% (Udeh *et al.*, 2014; Menendez *et al.*, 2015), reflecting the accuracy of physician-induced ischemia monitoring and diagnostics. According to today's practice, most patients return to surgical wards within hours of surgery and thereafter their vital parameters are monitored at four to eight hours' intervals in contrast to continuous intraoperative monitoring. Furthermore, postoperative analgesic medication and primary diseases, such as diabetes, blunt of the patient awareness and mask cardiac symptoms. Because of this, timely diagnosis and appropriate treatment of perioperative myocardial ischemia are challenging. Therapeutic guidelines designed for nonoperative myocardial infarction (MI) are not directly applicable because of the potential risk of postoperative bleeding. However, especially patients with cardiovascular risk factors, i.e. advanced age, coronary artery disease (CAD), renal insufficiency, peripheral artery disease (PAD), and diabetes, would benefit from intensified perioperative monitoring to detect and treat earlier hemodynamic disturbances, such as tachycardia, hypotension and hypoxemia, shown to increase the risk for myocardial ischemia (Mauermann *et al.,* 2016). Further studies are needed to determine the appropriate thresholds requiring intervention and to find safe and efficient treatment strategies.

To date, there is no specific treatment for PMI. Foucrier et al. (2014) investigated the effect of early cardiovascular therapy intensification in vascular surgery patients with postoperative troponin elevation and demonstrated that intensification of secondary prevention reduced the risk for long-term adverse cardiac outcomes. However, the patients whose treatment remained unchanged had a significantly higher risk for adverse cardiac outcomes (Foucrier et al., 2014). Despite these findings, further cardiac examinations or cardiovascular therapy intensification are seldom applied to patients with perioperative myocardial ischemia. Because the treatment of PMI is complex, prevention seems an appropriate strategy and it has been investigated in several large-scale studies (Devereaux et al., 2008; Devereaux et al., 2014; Devereaux et al., 2014). More recently, anticoagulants alone or combined with aspirin have been shown to be effective in reducing adverse cardiovascular events in high cardiac risk surgical patients (Devereaux et al., 2018; Steffel et al., 2020; Bonaca et al., 2020). However, data on efficacy and safety of these treatments remain limited and widely adapted recommendations do not exist.

Despite general advancements in perioperative care, mortality associated with PMI is still close to that observed 30 years ago (von Knorring, 1981). Furthermore, the exact pathophysiological mechanisms of perioperative myocardial ischemia are unclear.

Accordingly, the aims of this study were to elucidate the clinical picture and prognosis of PMI in a Finnish tertiary care university hospital, and to determine how a modern cardiac risk index (Gupta *et al.*, 2011) performs in predicting PMI in the particular patient cohort. Moreover, this thesis aimed to investigate the clinical significance of silent postoperative ischemia and acute endothelial injury and their association with development of PMI. Finally, this thesis included a systematic review and meta-analysis that aimed to determine the efficacy and safety of ultra-short-acting, cardio-selective beta-blocker esmolol in perioperative cardiac protection.

REVIEW OF THE LITERATURE

PERIOPERATIVE CARDIAC COMPLICATIONS IN NON-CARDIAC SURGERY

Perioperative myocardial infarction

The first observations about perioperative cardiac morbidity and its association with postoperative outcome date back to 1952, when PMI was first identified as a problem by American internist Felix Wroblewski and colleagues (Wroblewski and Ladue, 1952). The first observational studies reported incidence rates of 0.1% to 37% for PMI, depending on the patient population being studied. In the general population, PMI is rare, early studies reported an incidence of 0.1% to 0.7% (Tarhan *et al*., 1972; Plumlee and Boettner, 1972) which corresponds to today's observations (Udeh *et al.,* 2014; Menendez *et al.*, 2015). However, in high-risk patients the incidence of PMI is substantially higher, with studies from the 1960s to the 1980s showing that 1.9% to 37% of patients with CAD and previous myocardial infarction had a PMI in non-cardiac surgery (Tarhan *et al.*, 1972; Rao *et al.*, 1983; Goldman *et al.*, 1977; Steen *et al.*, 1978). Different types of surgeries carry a different cardiac risk. As early as in 1961, Driscoll and colleagues observed that patients with peripheral vascular disease were at a higher risk of sustaining PMI than the general population (Driscoll *et al*., 1961).

Since then, this observation has been confirmed by many investigators, and according to these studies the incidence of PMI in vascular surgery patients is 1% to 15% (McFalls *et al.*, 2008; Boucher *et al.*, 1985; Brown *et al.*, 1981; Hertzer, 1982; Yang *et al*., 2006). This is likely related to the burden of systemic atherosclerosis and CAD in this specific patient population (Sukhija *et al.*, 2004). Furthermore, surgery-related factors, such as clamping the arteries, bleeding, and a potentially prolonged operation with unstable hemodynamics, add to the increased cardiac risk.

In Finland, the incidence rates of PMI are similar to those observed in other Western countries. In 1981, von Knorring published the results of a prospective observational study of 12 654 patients undergoing non-cardiac surgery and reported an incidence of 1.8% for PMI. However, when 214 patients from the same cohort with previous myocardial infarction or electrocardiographic patterns suggesting myocardial strain were re-examined with systematic electrocardiography (ECG) monitoring at the time of their next operation, 17.7% of the patients were diagnosed with PMI, being fatal in 32% (von Knorring, 1981). This study still remains the largest investigating the incidence of PMI in Finnish non-cardiac surgery patients, but most likely does not fully reflect today's clinical situation since improvements have been made in the diagnostics and treatment of CAD. Since 1981, several

observational single-center studies investigating cardiac complications in non-cardiac surgery in Finland have emerged (Hietala *et al.*, 2014; Utriainen *et al.*, 2014; Hietala *et al.*, 2013; Scheinin *et al.*, 2000; Backlund *et al.*, 1999; Backlund *et al.*, 1999; von Knorring *et al.*, 1992). However, all of the studies have had inadequate sample size to reach any statistically significant results in clinically relevant patient-centered outcomes, and currently, no national guidelines exist regarding the perioperative monitoring or follow-up of patients with increased cardiac risk.

Perioperative myocardial ischemia

Perioperative myocardial ischemia, detected by continuous ECG monitoring, transesophageal echocardiography, cardiokymography, or changes in the blood lactate levels, gained researchers' attention in 1980. Early studies focused on intraoperative myocardial ischemia and reported incidence rates of 18% to 78% in patients with pre-existing CAD (London *et al.*, 1988; Stone *et al.*, 1988; Haggmark *et al.*, 1989). In 1990, monitoring started to be conducted through the postoperative period, and the first evidence of the relation of perioperative myocardial ischemia to postoperative outcome emerged. These studies showed that perioperative myocardial ischemia occurs most commonly postoperatively, (Mangano *et al.*, 1990) is silent in nature (Frank *et al.*, 1990; Ganz *et al.*, 1994), and is associated with postoperative cardiac complications (Frank *et al.*, 1990; Ganz *et al.*, 1994; Landesberg *et al.*, 1993; Landesberg *et al.*, 2001). However, debate continues about whether and how the potential perioperative myocardial ischemia should be monitored and whether treatment of ischemia can improve postoperative outcome.

Table 1 summarizes the studies investigating perioperative myocardial ischemia and its impact on postoperative outcome.

Table 1. *Studies investigating perioperative myocardial ischemia and its impact on postoperative outcome by continuous electrocardiographic monitoring.*

Study	N	Study type	Subject	Monitoring	Definition of ischemia	Outcomes	Results	Comments
Stone *et al.* 1988	89/39	RCT	Incidence of intraoperative myocardial ischemia in hyper-tensive patients with/ without single dose beta blocker premedication	V5	ST-segment depression ≥ 1mm, lasting > 1min	Incidence of intraoperative	28% of patients without premedication and 2% of patients with premedication had ischemic episodes ($p<0.01$). Tachycardia associated with ischemic events	Premedcated patients had more bradycardia and hypotension

Table 1. *Studies investigating perioperative myocardial ischemia and its impact on postoperative outcome by continuous electrocardiographic monitoring.*

London *et al.* 1988	105	Observational	Optimal ECG lead combination for detection of intraoperative myocardial ischemia in patients with known/suspected CAD	12-lead ECG. CK/	Premedicated patients had more bradycardia and hypotension	Incidence of intraoperative myocardial ischemia	24% of patients had ischemic events. Ischemia detection sensitivity of 96% was acquired by combining leads II, V4 and V5. 3 PMIs occurred (1 fatal), all PMIs associated with intraoperative ischemia	
McCann *et al.* 1989	50	Observational	Incidence of perioperative myocardial ischemia in patients undergoing elective lower-extremity revascularization	V5	ST-segment depression ≥ 1mm, lasting > 40s	Incidence of perioperative ischemia and adverse cardiac events	38% of patients had ischemic episodes. 95% of ischemia was asymptomatic. Tachycardia associated with ischemic episodes. 4 adverse cardiac events occurred, all in patients with ischemia ($p<0.02$)	Small sample size, vascular surgery
Ouyang *et al.* 1989	24	Observational	Incidence of perioperative myocardial ischemia in patients with stable CAD undergoing peripheral vascular surgery	4-lead cECG. A 12-lead ECG and CK-MB	ST-segment sift ≥ 1mm, lasting > 2min	Incidence of perioperative ischemia and adverse cardiac events	63% of patients had ischemic episodes. Patients with/without ischemia did not differ in terms of hemodynamic changes. Patients with ischemia had significantly more adverse cardiac events ($p<0.05$)	Small sample size, vascular surgery
Pasternack *et al.* 1989	200	Observational	Incidence of perioperative myocardial ischemia in patients undergoing major arterial and CEA surgeries	ND	ND	Incidence of perioperative ischemia and adverse cardiac events	64% of patients had ischemic episodes. 9 patients had PMI. Patients suffering PMI had significantly more ischemia compared to the patients without PMI ($p\leq0.05$)	Vascular surgery

Table 1. *Studies investigating perioperative myocardial ischemia and its impact on postoperative outcome by continuous electrocardiographic monitoring.*

Hägg-mark *et al.* 1989	53	Obser-vational	The accuracy of ECG, cardio-kymography myocardial lactate and intra-operative hemo-dy-namic data in detection of intra-operative myocardial ischemia	CKG, ECG (V5), LAD lactate extraction, PCWP	1) ST-segment depression ≥ 1mm or ST-segment elevation ≥ 2mm and 2) change from type I to type II or III in CKG in at least 3 consecu-tive beats and/or 3) myocardial lactate pro-duction	Incidence of intra-operative myocardial ischemia	74% of the patients had is-chemic events. Patients with an abnormal preoperative ECG had more ischemic events ($p<0.01$). 83% of ischemic events were detected by CKG, 44% by ECG, and 15% by myocardial lactate produc-tion. Changes in PCWP did not associate with ischemia.	Small sample size, major vascular surgery
Frank *et al.* 1990	1	Case report	A case report of a 62-year-old man undergoing peripheral vascular sur-gery.	II, V5	ST-segment depression ≥ 1mm	ND	The patient had ST-segment depression-type ischemia that associated with tachycardia. I.v esmolol was ini-tiated. Esmolol decreased BP but not HR and was discontinued. Ischemia increased, and the patient suffered cardiac arrest	Case report
Man-gano *et al.* 1990	474	Obser-vational	Incidence of peri-operative myocardial ischemia in men with or at risk for CAD undergoing noncardiac surgery	3-lead cECG	ST-segment depression ≥ 1mm or ST-segment elevation ≥ 2mm, last-ing ≥ 1min	Adverse cardiac events	41% of patients had postop-erative ischemic episodes which associated with a significant increase of the odds for adverse cardiac out-comes, espe-cially cardiac death, non-fatal MI and UAP.	
Man-gano *et al.* 1991	100	Obser-vational	Incidence of peri-operative myocardial ischemia in patients with or at risk for CAD undergoing noncardiac surgery	3-lead cECG. Ische-mic signs and symp-toms	ST-segment depression ≥ 1mm or ST-segment elevation ≥ 2mm, last-ing ≥ 1min	Adverse cardiac events	28 patients had preoperative, 27 patients had intraoperative and 42 patients had postopera-tive ischemia. 94% of ischemia was silent. Is-chemia did not associate with hemodynamic changes. 13% of patients had an adverse cardiac event, 84.6% of the events associated with ischemia.	

Table 1. *Studies investigating perioperative myocardial ischemia and its impact on postoperative outcome by continuous electrocardiographic monitoring.*

Mangano *et al.* 1991	100	Observational	Incidence of perioperative myocardial ischemia in patients with or at risk for CAD undergoing noncardiac surgery	V5	ST-segment depression ≥ 1mm or ST-segment elevation ≥ 2mm, lasting ≥ 1min	Adverse cardiac outcomes: Cardiac death, nonfatal MI, UAP, heart failure caused primarily by a cardiac condition	27% of patients had postoperative ischemia. Ischemia was most severe during the early (days 0-3) vs. late (days 4-7) postoperative period. Most ischemic episodes (57%) were associated with tachycardia	
Landesberg *et al.* 1993	151	Observational	Incidence of perioperative myocardial ischemia in patients undergoing major vascular surgery	3-lead cECG. A 12-lead ECG and CK-MB	ST-segment depression ≥ 1mm or ST-segment elevation ≥ 2mm, lasting ≥ 1min	Adverse cardiac outcomes: MI, UAP, and heart failure	58% of the patients had periopertive ischemic events. 91% of the ischemia was asymptomatic. Postoperative ischemic events were longer compared to pre- and intraoperative events ($p<0.01$) and associated with adverse cardiac outcomes ($p<0.01$)	Vascular surgery
Ganz *et al.* 1994	1	Case report	A case report of an 87-year-old man undergoing CEA	cECG (leads not defined) CK-MB	ND	ND	Preoperative cECG had 8 asymptomatic ischemic events which were preceded by a rise of the HR. On 2nd postoperative day, patient was found in ventricular fibrillation and suffered cardiac arrest. Postoperative cECG had marked ischemia throughout postoperative period.	Case report
Landesberg *et al.* 2001	185	Observational	Incidence of perioperative myocardial ischemia in patients undergoing major vascular surgery	12-lead cECG, CK-MB and TnI	ST-segment depression or elevation ≥ 2mm in one lead or ≥ 1mm in two contiguous leads, lasting ≥ 10min	Cardiac death, myocardial infarction	21% of the patients had perioperative ischemic events. 12 patients (6.5%) suffered PMI; 1 of those died. The duration of ischemic events was significantly longer in patients with PMI compared to those without PMI ($p<0.01$)	Vascular surgery

Table 1. *Studies investigating perioperative myocardial ischemia and its impact on postoperative outcome by continuous electrocardiographic monitoring.*

Landesberg *et al.* 2002	447	Observational	The long-term prognostic value of perioperatively measured cardiac biomarkers and cECG in patients undergoing vascular surgery	12-lead cECG, CK-MB and TnI and/or TnT	ST-segment depression or elevation ≥ 2mm in one lead or ≥ 1mm in two contiguous leads, lasting ≥ 10min	Cardiac death, myocardial infarction, long-term survival (follow-up 1 to five years)	Elevated postoperative CK-MB, TnI, TnT, and prolonged (>30min) ischemia predicted long-term mortality independently of the preoperative risk factors. Even slightly elevated (CK-MB>5%, TnI>0.6ng/ml, TnT>0.03ng/ml) increased long-term mortality	Vascular surgery
Raby *et al.* 1999	26	RCT	The effect of esmolol on the incidence of post-operative myocardial ischemia in patients at high cardiac risk undergoing vascular surgery	12-lead cECG, CK-MB	ST-segment depression ≥ 1mm, lasting ≥ 1min	Incidence of post-operative myocardial ischemia, cardiac death, PMI, UAP, heart failure	Ischemic threshold HR (min 60 bpm) for each patient was identified. 73% of the patients in the placebo group had postoperative ischemia, compared to 33% of the patients in the esmolol group ($p<0.05$). There were no differences regarding the other outcomes	The use of alternative beta blockers, antihypertensive medi-cation and analgesics was allowed in both groups
Urban et al. 2000	107	RCT	The effect of esmolol on the incidence of post-operative myocardial ischemia in patients at high cardiac risk undergoing elective total knee arthroplasty	7-lead cECG, CK-MB	ST-segment depression ≥ 1mm, lasting ≥ 1min	Incidence of post-operative myocardial ischemia, PMI, cardiac morbidity (chest pain, heart failure, UAP)	None of the patients in the esmolol group had postoperative ischemia, compared to 7% of the patients in the placebo group ($p<0.04$). After switching to metoprolol, the difference was not statistically significant. There were no differences regarding the other outcomes	Esmolol was switched to oral metoprolol on first postoperative day

Abbreviations: RCT, randomized controlled trial; ECG, electrocardiogram; CAD, coronary artery disease; CK, creatine phosphokinase; PMI, perioperative myocardial infarction; cECG, continuous electrocardiogram monitoring; CK-MB, creatine kinase MB-isoenzyme; ND, not defined; CKG, cardiokymography; LAD, left anterior descending coronary artery; PCWP, pulmonary capillary wedge pressure; ICU, intensive care unit; BP, blood pressure; HR, heart rate; MI, myocardial infarction; UAP unstable angina pectoris; TnI, cardiac troponin I; TnT, cardiac troponin T; CABG, coronary artery bypass graft surgery; AF, atrial fibrillation.

Myocardial injury in non-cardiac surgery

The latest update on the sequelae of perioperative cardiac morbidity came in 2014, when Botto and colleagues introduced the definition of myocardial injury in non-cardiac surgery (MINS). The authors defined MINS as a myocardial injury that may or may not result in necrosis, has prognostic significance and occurs within 30 days of non-cardiac surgery, based on the prospective analysis of the perioperative clinical data of over 15 000 patients (Botto *et al*., 2014). The introduction of MINS expanded previous knowledge of perioperative cardiac complications by showing that a mere perioperative cardiac biomarker release, irrespective of other ischemic features, is associated with substantial cardiovascular morbidity and mortality (Devereaux *et al*., 2017). Puelacher *et al.* (2018) confirmed this observation in a separate cohort of patients. It remains unclear, however, whether or not the risk of mortality imposed by MINS is modifiable, and if so, by which treatment. Currently, several trials targeting both MINS prevention and treatment are underway; results can be expected in the near future.

Morbidity and mortality

Since the initial observation of perioperative cardiac complications, it was clear that a substantial mortality is associated with these events. Studies from the early 1990s reported a mortality of 36% to 70% associated with PMI (Mangano, 1990; Mangano *et al*., 1990; Mangano *et al*., 1991; Raby *et al*., 1992). More recently, mortality rates of 12% to 40% have been reported (Devereaux *et al*., 2011; Davenport *et al.*, 2007; Ghaferi *et al*., 2009; Devereaux *et al*., 2005). The decreased mortality may be the result of overall improved perioperative care, including patient selection, preoperative optimization and improved management of perioperative complications. However, patients with PMI still have a tenfold 30-day mortality relative to patients without PMI (Redfern *et al*., 2011). Furthermore, studies from the past five years have demonstrated that even a minor perioperative cardiac troponin release is associated with increased mortality. For example, Devereaux and colleagues showed that a troponin T (TnT) release of 0.02 ng/mL had an adjusted hazard ratio (aHR) of 2.41 (95% CI: 1.33-3.77) for 30-day mortality compared with a TnT concentration of 0.01 ng/mL or less. Higher concentrations of 0.02-0.029 ng/mL and >0.03 ng/mL had aHRs of 5 (95% CI 3.72-6.76) and 10.48 (95% CI 6.25-16.62), respectively. Mortality rates for TnT concentrations of 0.01, 0.02, 0.02-0.029, and >0.03 were 1.0,% 4.0%, 9.3%, and 16.3% (Devereaux et al., 2012).

Already in 1983 intensified perioperative monitoring, prolonged stay in intensive care unit (ICU), and timely management of hemodynamical disturbances were suggested for high cardiac risk patients undergoing non-cardiac surgery (Rao *et al*., 1983). Despite this early idea of intensified monitoring, high cardiac risk patients are today most commonly monitored in the same manner as the general surgical population and postoperative cardiac complications remain underdiagnosed and inadequately managed.

BASIC PATHOPHYSIOLOGY OF PERIOPERATIVE MYOCARDIAL INFARCTION

Despite years of research, the exact pathophysiological mechanisms of perioperative cardiac complications are still generally poorly understood. Surgery and anesthesia are associated with activation of the sympathetic nervous system, inflammation, hypercoagulability, hemodynamic disturbances, bleeding and hypothermia, all of which are elements that destabilize a previously balanced CAD and can trigger cardiac complications. Data from several perioperative hemodynamic studies suggest that tachycardia precedes ischemic episodes (Biccard and Rodseth, 2010) and is today a generally recognized element in the pathophysiology of perioperative cardiac ischemia. In addition, according to the current evidence coronary hypoperfusion and thrombus formation may play a key role in this pathophysiological process.

Timing of presentation

The identification of PMI depends on the laboratory measurement used. Studies conducted in the 1980s, in which the diagnosis was set based on repeated postoperative ECG recordings, suggested that PMIs occur on the second or third postoperative day. Moreover, the earlier studies generally used creatine phosphokinase (CK) as the biomarker of cardiac injury. Especially at the beginning, the laboratory analysis of this biomarker was slow, and furthermore, CK is not totally cardiac-specific but is expressed in skeletal muscles, brain, and several other tissues (Rosalki *et al*., 2004). Today, with cardiac troponins being the most commonly used biomarkers, most PMIs are identified within the first two postoperative days (Badner *et al.*, 1998; Gandhi *et al*., 2006).

Figure 1 presents the kinetics of the different cardiac biomarkers in acute MI.

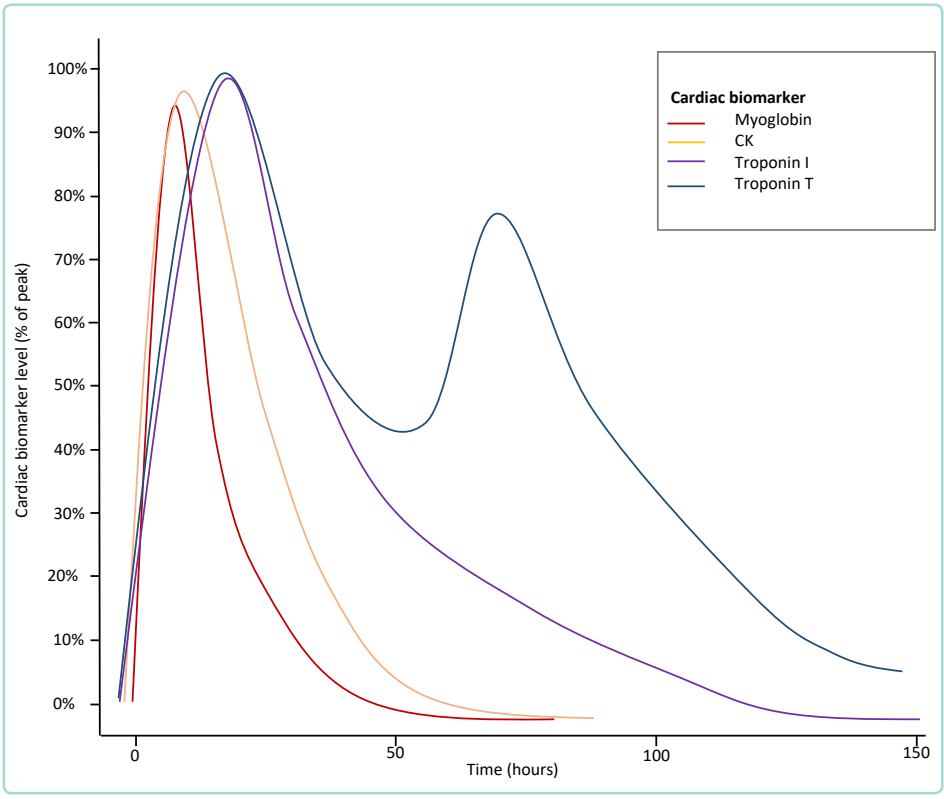

Figure 1. *The kinetics of the different cardiac biomarkers in acute myocardial infarction. Elements of the figure adapted from original publication by Laugaudin et al. (Laugaudin et al., Kinetics of high-sensitivity cardiac troponin T and I differ in patients with ST-segment elevation myocardial infarction treated by primary coronary intervention. Eur Heart J Acute Cardiovasc Care 2016;5:354-363.)*

Different types of myocardial infarction

In the third universal definition of myocardial infarction, different types have been identified (Thygesen *et al.*, 2012), with type 1 and type 2 being predominant in the non-cardiac operative setting.

Figure 2 demonstrates the difference between type 1 and type 2 MIs.

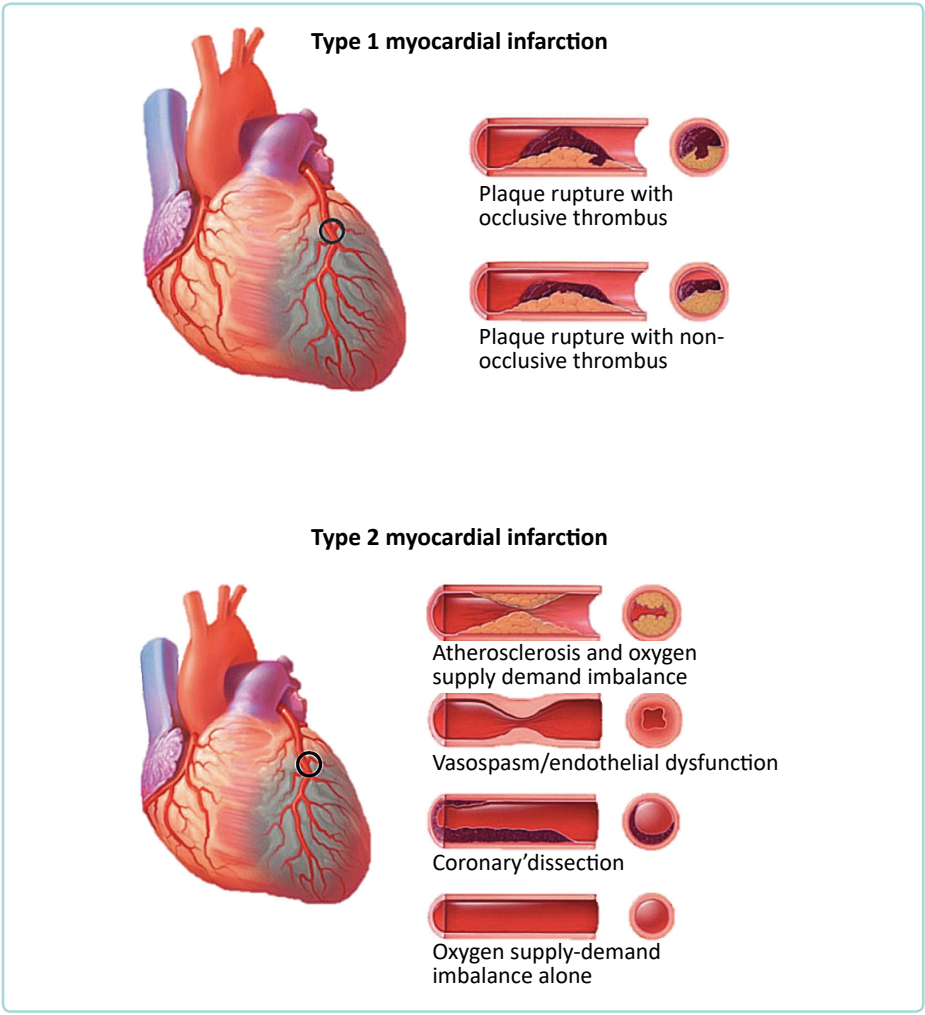

Figure 2. *Type 1 and type 2 myocardial infarction. Elements of the figure adapted from original publication by Thygesen et al. (Thygesen et al., Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581-1598.)*

Classically, the majority of PMIs have been considered to be of type 2, however, recent post-mortem and angiographic studies have shown that the difference compared with nonoperative MIs is not as significant as previously thought (Gualandro *et al*., 2012).

Type 1 myocardial infarction

Type 1 MI is an event related to atherosclerotic plaque rupture, ulceration, or dissection that results in intraluminal thrombus in one or more coronary arteries. This cascade leads to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis (Thygesen *et al.*, 2012). Of fatal MIs in nonoperative settings, 70% are associated with coronary plaque rupture and usually patients present with severe CAD. However, on occasion (5-20% of cases) only mild to moderate or no CAD is found in coronary angiography, especially in women (Thygesen *et al.*, 2012). Post-mortem and angiographic studies have shown that in 40% to 50% of patients sustaining fatal PMI either atherosclerotic plaque rupture or coronary thrombus is present (Cohen and Aretz, 1999; Duvall *et al.*, 2012). Thus, although type 2 MI might dominate in the perioperative setting, the difference is not as significant as estimated in the review articles.

Established CAD with complex coronary lesions appears to be an important predisposing factor for PMI. Fatal PMIs due to an atherosclerotic plaque rupture seem to occur randomly throughout the first 17 postoperative days (Cohen and Aretz, 1999; Dawood *et al.*, 1996). However, of all PMIs only 7% have the etiology of ruptured atherosclerotic plaque and subsequent coronary thrombus (Gualandro *et al.*, 2012). Thus far, the only study comparing nonoperative and perioperative MIs was published by Gualandro and colleagues in 2012. According to their findings, up to 45% of the patients with PMI had angiographic evidence of complex coronary lesions suggestive of type 1 MI, compared with 57% of the patients with non-operative MIs. Notably, even in the presence of clear coronary obstruction only 40% of patients with PMI had typical ischemic symptoms (Gualandro *et al.*, 2012).

To summarize, in light of the current evidence type 1 MI appears to be somewhat less common than type 2 MI in the operative setting. However, the difference between the incidences might not be as clear as previously thought. Furthermore, the current histological observations may not be totally accurate since patients with PMI are generally referred for coronary angiography significantly later than patients with non-operative MIs (Gualandro *et al.*, 2012). This may result in prolonged exposure to antiplatelet or anticoagulant agents or potentially spontaneous resolution of thrombi.

Type 2 myocardial infarction

Type 2 MI is an event related to a condition other than plaque rupture that causes an imbalance between myocardial oxygen supply and demand. Type 2 MI may occur in critically ill or in patients undergoing major non-cardiac surgery when factors such as endogenous or exogenous catecholamines, endothelial dysfunction, coronary vasospasm, tachycardia, and hypertension or hypotension cause both an increased myocardial oxygen demand and a decreased coronary blood flow.

According to the post-mortem studies, approximately 50% of fatal PMIs are caused by myocardial oxygen supply-demand imbalance (Cohen and Aretz, 1999; Dawood *et al.*, 1996). Fatal PMIs caused by myocardial oxygen supply-demand imbalance predominate in the early (days one to four) postoperative period (Cohen and Aretz, 1999). Similarly to type 1 MIs, low-flow states secondary to coronary stenoses seem to be important in the development of type 2 PMI (Ellis *et al.*, 1996). However, in the operative setting the site of MI does not necessarily depend on the site of critical stenoses (Poldermans *et al.*, 2001), supporting the hypothesis that the pathophysiology of PMI differs from that of nonoperative MI. Furthermore, the majority of perioperative myocardial ischemia and MIs are of non-ST-segment elevation type. Perioperative ischemic events are usually transient but especially if prolonged, may lead into cardiac biomarker release and development of PMI (Landesberg *et al.*, 1993). Hemodynamic studies have demonstrated that an increase in heart rate or relative tachycardia usually precedes perioperative ischemic events (Fleisher *et al.*, 1995; Landesberg *et al.*, 2002). Other important aspect is that, unlike in a nonoperative setting, where hypertension and subsequent left ventricular enlargement have been shown to predict coronary plaque rupture, (Heidland and Strauer, 2001), hypotension is more commonly associated with adverse perioperative cardiac outcomes (Charlson *et al.*, 1989; Sprung *et al.*, 2000).

To summarize, the development of type 2 MI in non-cardiac surgery seems to be due to a complex interplay between pre-existing risk factors, perioperative hemodynamic disturbances and postoperative proinflammatory and hypercoagulability state. These mechanisms warrant further investigation to elucidate the pathophysiology of PMI.

Summary of pathophysiological mechanisms

Understanding the pathophysiological mechanisms of PMI is essential in order to develop appropriate prevention and treatment strategies. Based on the discussed studies, the following factors are probably responsible for the development of PMI: First, PMI is most likely to occur in patients with CAD or with several risk factors for CAD. Second, hemodynamic disturbances, namely tachycardia and/or hypotension, typical for intraoperative and immediate postoperative period cause patients to have a relative flow-mediated hypoperfusion, further aggravated by coronary thrombus secondary to hypercoagulability and inflammation. Furthermore, most patients have at least mild to moderate anemia postoperatively because of bleeding and dilution, and this further decreases the oxygen supply. Finally, myocardial oxygen demand is perioperatively increased because of pain, shivering, and sympathetic activation.

It is unknown by which mechanisms coronary occlusions occur in the perioperative setting, independently from plaque rupture or fissure. Virchow's triad is the classic model describing the factors predisposing to

thrombus formation and encompasses abnormalities of flow, endothelium, and coagulation (Lowe, 2004). According to this, the following key elements have been suggested in a review article by Biccard and Rodseth (2010). First, the pre-existing non-critical coronary stenoses, together with preoperative tachycardia and hypotension, create post-stenotic flow stasis due to a decreased blood velocity associated with a fall in the pressure gradient across the coronary artery. Second, coronary flow stagnation creates conditions favorable for thrombus formation. The cascade is initiated by platelet activation that occurs in high shear stress conditions, i.e. at the apex of stenosis. Activated platelets interact with each other causing platelet count to increase and platelet activation to rise exponentially. On entering the post-stenotic recirculation zone platelets are exposed to a low shear stress milieu, allowing cellular interaction and thrombus formation to take place (Biccard and Rodseth, 2010). Thrombus formation is further enhanced by changes in red blood cells and the endothelial glycocalyx and expression of coagulation factors. In the recirculation region, red blood cells undergo clumping and interact with both platelets and neutrophils, contributing to thrombus formation (Goel and Diamond, 2002).

Furthermore, at the location of the post-stenotic low shear stress zone, the endothelial glycocalyx undergoes an up-regulation of pro-inflammatory cytokines, increasing the expression of adhesion molecules, such as vascular adhesion molecule (V-CAM), intracellular adhesion molecule (I-CAM), and E-selectin, while down-regulating the production of endothelial nitric oxide synthetase (eNOS), prostacyclin, and tissue plasminogen activator (tPA) – factors all resulting in increased thrombogenicity (Biccard and Rodseth, 2010). Finally, in the postoperative period, there is a rise in all coagulation factors, e.g. fibrinogen increases by 50% to 100% (Longhitano *et al.*, 2006), increasing plasma viscosity, platelet aggregation, and platelet sensitivity to catecholamines. At the same time, coagulation inhibitors appear to be decreased, probably due to dilution or impaired synthesis (Longhitano *et al.*, 2006).

In summary, pre-existing coronary stenoses together with perioperative hemodynamic disturbances create zones of decreased blood flow velocity and low shear stress, ideal for platelet and endothelial activation and initiation of coagulation cascade. Confirmation of this hypothesis by future studies is essential since efficient prevention and treatment of perioperative cardiac complications depend on clearly elucidating the pathophysiology underlying these complications.

ENDOTHELIAL GLYCOCALYX IN CARDIAC DISEASE

Structure and function of endothelial glycocalyx

The glycocalyx, comprising glycoproteins, proteoglycans, and soluble proteins, coats the endothelium of all healthy vasculature. The presence of this structure was first documented by Danielli in 1940 (Danielli, 1940) and investigations of its physiological role began in 1970 (Desjardins and Duling, 1990). The endothelial glycocalyx (EG) was long regarded as a selective but static physical barrier maintaining vascular wall permeability and this was supported by Starling's law of capillary exchange in 1896 (Levick and Michel, 2010). Today, it is evident, however, that EG is a dynamic biochemical structure that in physiological conditions regulates vascular permeability, cellular interactions, coagulation, thrombosis, and inflammation, and acts as a mechanosensor of fluid shear stress that controls vascular tone.

Figure 3A presents the basic structure of normal EG.

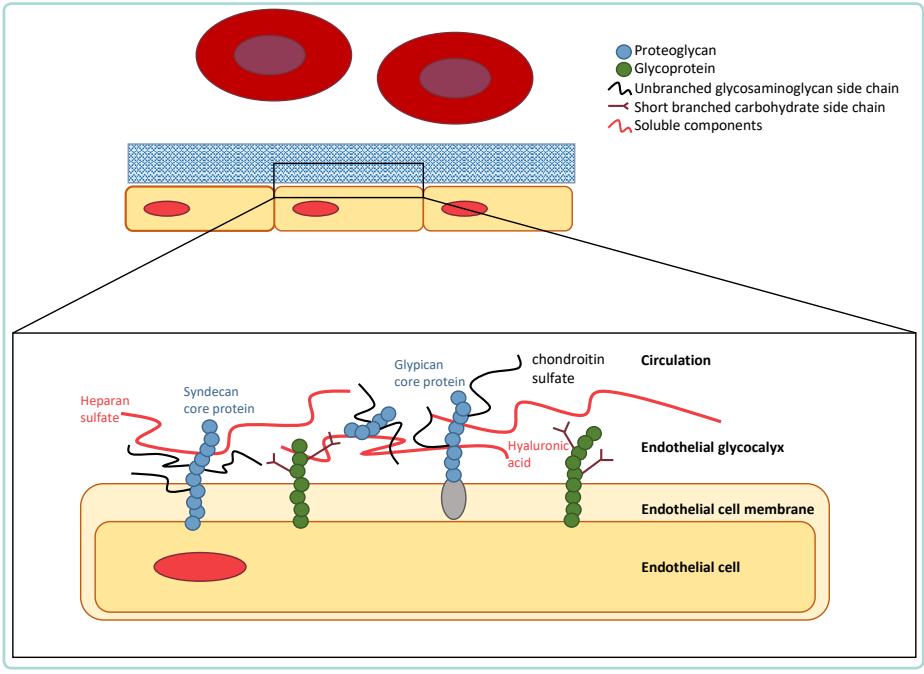

Figure 3A. *The basic structure of endothelial glycocalyx. Elements of the figure adapted from original publications by Schött et al. and by Iba and Levy. (Schött et al., The endothelial glycocalyx and its disruption, protection and regeneration: a narrative review. Scand J Trauma Resusc Emerg Med 2016;24:48; Iba and Levy. Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost 2019;17:283-294.)*

Proteoglycans and glycoproteins anchor the glycocalyx to the endothelium and form an extensive matrix containing soluble plasma components (Pillinger and Kam, 2017). Proteoglycans have a protein core to which negatively charged glycosaminoglycan (GAG) side chains are attached. The proteoglycan core proteins may be attached to the endothelial cell membrane (e.g. glypicans) or have a transmembrane domain that links to the endothelial cell cytoskeleton (e.g. syndecans), while the GAG chains extend into the extracellular space (Tarbell and Cancel, 2016). Heparan sulfate (HS), chondroitin sulfate (CS), and hyaluronan (HA) are the dominant GAGs on most cell surfaces (Tarbell and Cancel, 2016). The GAG chains carry strong negative charge and are hydrophilic. Glycoproteins are glycoconjugates in which a core protein carries one or more glycans covalently attached to a polypeptide backbone. Common examples of glycoproteins are endothelial cell surface receptors that contribute to leukocyte adhesion during inflammation, including selectins (E and P), integrins, and members of the immunoglobulin superfamily (e.g. I-CAM and V-CAM) (Tarbell *et al*., 2014). The EG interacts with several soluble plasma constituents, such as proteins (e.g. albumin), growth factors and ions forming a dynamic, physiologically active layer known as the endothelial surface layer (ESL) (Tarbell and Cancel, 2016). The entire makeup of the ESL continuously changes with a process of destruction and re-synthesis occurring at the interface between flowing blood and soluble components within the ESL (Reitsma *et al*., 2007).

As a complex and active composite of inert glycocalyx and bound plasma constituents, ESL plays an important role in several physiological processes. ESL regulates vascular permeability and fluid filtration through the capillary walls. The process is regulated at the site at which it begins in the capillary network, and ESL tightly controls the oncotic pressure differences between vascular lumen and surrounding tissue, thereby leading to less fluid filtration (Becker *et al*., 2010). In addition to maintaining fluid homeostasis, ESL regulates cellular interactions by repelling red blood cells (Reitsma *et al*., 2007) and attenuating the interactions of platelets and leukocytes (Becker et al., 2010). ESL protects endothelial cells from the shear stress of blood flow (Pries *et al*., 2000). Increased shear stress activates ESL to produce nitric oxide (NO) which causes vasodilatation and reduces shear stress (Jacob *et al*., 2007). Furthermore, ESL protects the endothelial cells from oxidative stress through its capacity to bind enzymes that scavenge oxygen radicals (Reitsma *et al*., 2007) Finally, ESL binds several ligands and enzymes facilitating cellular signaling and enzymatic modification (Reitsma *et al*., 2007), and important anticoagulant mediators such as antithrombin III (Alphonsus and Rodseth, 2014). The endothelium also participates in the production of anticoagulant mediators itself, and functional endothelium and ESL are essential in maintaining homeostasis in coagulation and anticoagulation.

Endothelial glycocalyx injury

As EG interacts and dynamically reacts to the different circulating plasma constituents and physiological changes, it may shed or destroy under a variety of conditions. Figure 3B demonstrates the rearrangement and shedding of EG following a noxious stimulus.

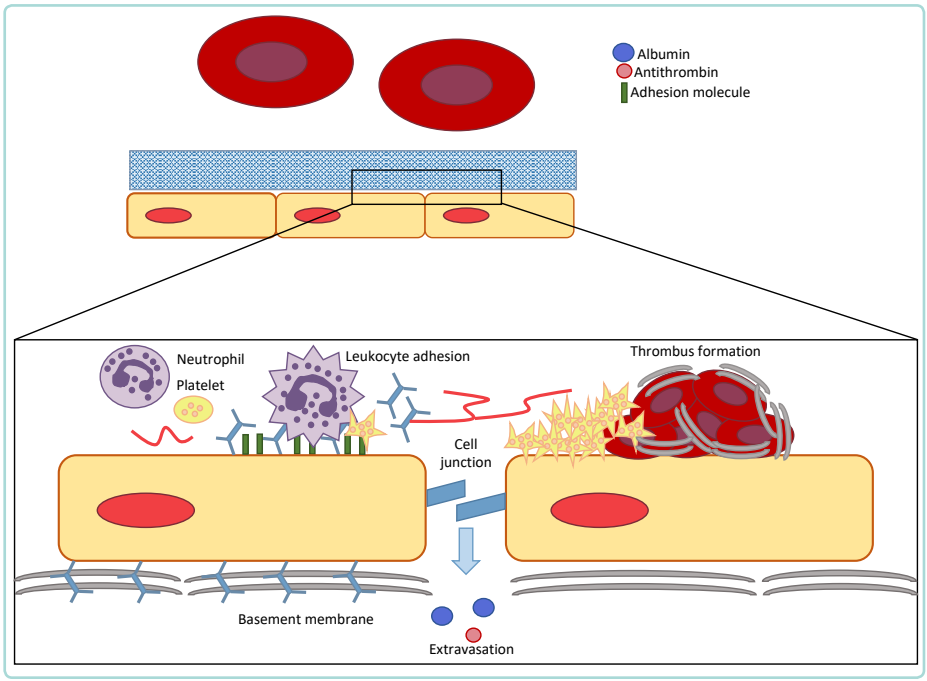

Figure 3B. *Vascular endothelial damage and derangement of glycocalyx. Elements of the figure adapted from original publications by Schött et al. and by Iba and Levy. (Schött et al., The endothelial glycocalyx and its disruption, protection and regeneration: a narrative review. Scand J Trauma Resusc Emerg Med 2016;24:48; Iba and Levy. Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost 2019;17:283-294.)*

Endothelial glycocalyx injury can vary from relatively minor perturbations to a complete dissolution of the layer. Any damage can lead to adverse consequences such as increased vascular wall permeability and interstitial edema, attenuated vascular responses to shear stress, platelet aggregation, leukocyte adhesion, altered microvascular blood viscosity and generation of prothrombotic milieu. Furthermore, these adverse alterations of physiology have been shown to be associated with a variety of diseases. For example, normal renal function depends upon an intact glycocalyx, and atherogenesis seems to be associated with glycocalyx injury (Alphonsus and Rodseth, 2014).

Pathological injury to EG may occur in a several clinical conditions. Thus far, our knowledge of the pathophysiological mechanisms leading to EG injury in these specific conditions comes largely from animal and in vitro studies.

Ischemia-reperfusion (I/R) injury. A marked decrease in the endothelial glycocalyx GAG chain volume has been observed after I/R (Mulivor and Lipowsky, 2004). EG destruction related to I/R may particularly be a concern in cardiac surgery since this impairs endothelial-dependent coronary vasodilatation and is associated with a no-reflow phenomenon and interstitial edema (Chappell et al., 2009). In fact, cardiac surgery itself has been shown to predispose to EG diminution, independently from I/R, as shown by Bruegger et al. (2009). EG injury following I/R is not solely restricted to the heart, but concerns also other vital organs, such as the liver and kidneys (Park *et al.*, 2010; Snoeijs *et al., 2011).*

Sepsis and trauma. Inflammatory mediators, such as tumor necrosis factor alpha (TNF- α),), cause glycocalyx shedding in sepsis, trauma and inflammation. Other mediators associated with EG injury in these conditions include C-reactive protein (CRP), adenosine, bradykinin, and bacterial lipopolysaccharide (Pillinger and Kam, 2017). The absolute plasma level of syndecan-1 has been shown to correlate with severity of sepsis, dismal prognosis and need for intubation in septic shock patients (Puskarich *et al.*, 2016). Because of the generalized nature of septic disease, studies have focused on measuring the leaked EG components from plasma, rather than demonstrating the EG injury in a specific organ.

Hypervolemia. Fluid volume overload can independently cause endothelial shedding. When colloid solutions are infused in normovolemic patients, approximately 60% of colloid almost immediately extravasates into the interstitial space (Pillinger and Kam, 2017). Furthermore, atrial natriuretic peptide (ANP) has direct adverse effects on glycocalyx integrity. ANP is secreted from the atria as a response to increased fluid shear stress and causes a rapid shedding of glycocalyx via a cyclic-GMP-linked proteolytic pathway (Bruegger *et al.*, 2005).

Blood volume loss. Like hypervolemia, also hypovolemia, or more accurately severe bleeding, has been shown to cause glycocalyx shedding. Current observations are based on animal studies. Kozar *et al.* (2011) demonstrated a significant glycocalyx volume loss when rats were subjected to bloodletting and subsequent severe hypotension (mean arterial pressure of 30 mmHg in 90 minutes). The changes were partially restored with plasma resuscitation, but not when crystalloids were used. In another study by Torres Filho *et al.* (2013), a 40% reduction in circulating blood volume caused a 59% reduction in glycocalyx thickness. Based on these in vitro observations, EG injury has been suggested to play a key role in the development of hemorrhagic shock.

Hyperglycemia. Both acute and chronic hyperglycemias have been shown to damage the glycocalyx. During acute hyperglycemia a reduction in glycocalyx volume and an increased glycocalyx permeability have been demonstrated in both animal (Zuurbier *et al.*, 2005) and clinical studies (Nieuwdorp *et al.*,

2006). Both of the forementioned studies concluded that hyaluronans, critical in maintaining the glycocalyx integrity, seem to be the vulnerable component during acute hyperglycemia. Clinical studies investigating diabetic patients have shown that these patients lose approximately half to three-quarters of their systemic glycocalyx volume compared with age-matched controls (Nieuwdorp *et al.*, 2006). Furthermore, shedding of the glycocalyx has been postulated to be associated with development of microalbuminuria (Singh *et al.*, 2011). The exact mechanisms connecting hyperglycemia and EG injury remain unknown. Reactive oxygen species disrupting hyaluronan binding to the glycocalyx, modulation of the sulfation of GAG chains, and a decrease in the number of GAG chains have been hypothesized to be the key elements (Lemkes *et al.*, 2012).

Endothelial glycocalyx in chronic and acute cardiovascular disease

Atherosclerosis is an inflammatory disease. For long, the process of atherogenesis has been considered by many to be dependent on the accumulation of lipids within the artery wall. Today, however, it is evident that the pathology of atherosclerosis is far more complicated than previously supposed. Despite changes in lifestyle and the use of cholesterol-lowering medication, cardiovascular diseases continue to be the leading cause of death in developed countries (Braunwald, 1997). Based on numerous pathophysiological observations, the response-to-injury hypothesis of atherosclerosis was formulated as early as in the 1970s (Ross and Glomset, 1973). This hypothesis initially suggested endothelial denudation as the first step in the development of atherosclerosis, but today endothelial dysfunction, rather than denudation, is emphasized (Ross, 1999).

Regardless of the exact mechanism of endothelial injury, following loss of homeostasis in large and medium-sized muscular arteries, each characteristic lesion of atherosclerosis represents a different stage of chronic inflammation in an artery wall; if the process is unabated and excessive it can lead to complicated lesions and sequelae such as myocardial ischemia. The possible mechanisms of endothelial dysfunction have been discussed earlier in this section. In the case of atherosclerosis, elevated and modified low-density lipoprotein (LDL) concentrations, free oxygen radicals caused by cigarette smoking, hypertension, diabetes, genetic alterations, elevated homocysteine concentrations, and certain micro-organisms have been suggested to predispose to endothelial dysfunction (Ross, 1999). Regardless of the underlying mechanism or their combination, atherosclerosis is highly a characteristic response to endothelial dysfunction in certain arteries (Ross, 1993). Endothelial injury and subsequent dysfunction start a series of compensatory mechanisms that alter the normal homeostatic properties of the endothelium. First, endothelial adhesiveness with respect to leukocytes, mainly monocyte-derived macrophages and T-lymphocytes, and platelets and

its permeability increase. Furthermore, the normally anticoagulant properties of the endothelium become procoagulant, and vasoactive molecules, cytokines, and growth factors are produced. If the inflammatory reaction is not able to repel or neutralize the offending agents, the process keeps going and stimulates migration and proliferation of smooth muscle cells at the area of inflammation and eventually an intermediate lesion is formed. These lesions may thicken the artery wall. However, during the initial stages thickening is compensated by gradual dilatation of the artery wall and the diameter of the lumen remains unchanged (Glagov et al., 1987). Continuous cycles of accumulation of mononuclear cells, migration and proliferation of smooth muscle cells, and formation of fibrous tissue lead to further enlargement and remodeling of the lesion, it becomes covered by a fibrous cap, and an advanced complicated lesion is formed. At some point, the compensatory mechanisms dilating the artery lumen will be lost and the lesion will obstruct the lumen and alter the blood flow.

Taking the previous observations into account, endothelial dysfunction is today regarded as a clinical syndrome that is independently associated with and predicts adverse cardiac events. One of the most important factors in this cascade may be the reduced NO production and impaired vasodilatation, characteristic of a dysfunctional endothelium. Several studies (Egashira *et al.*, 1993; Motz *et al.*, 1991; Quyyumi *et al.*, 1992; Zeiher *et al.*, 1995) have demonstrated an association between the presence of coronary microvascular endothelial dysfunction and symptoms of angina pectoris in individuals with normal coronary angiography findings. Furthermore, Zeiher *et al.* (1995) showed an association between impaired coronary endothelium-dependent vasodilatation and exercise-induced myocardial perfusion defects in individuals without clinically relevant CAD. In addition to ischemic symptoms and transient myocardial ischemia, endothelial dysfunction may have a fundamental role in the development of acute coronary syndrome (ACS), including acute myocardial infarction. Plaque destabilization and rupture comprise a detrimental process usually leading to the most severe cardiac complications. This process is a complex interplay of inflammatory effects that include cellular plaque components and inflammatory mediators (Libby *et al.*, 2002). Endothelial dysfunction may contribute to plaque destabilization in several ways. A dysfunctional endothelium is associated with increased oxidative stress and on the other hand, decreased NO bioavailability (Bonetti *et al.*, 2003). Both of these factors together and independently promote the inflammatory process that destabilizes the plaque. Increased vasoreactivity favoring local vasoconstriction decreases coronary blood flow and may represent a physical trigger for plaque rupture (Bogaty *et al.*, 1994). Finally, endothelial dysfunction is characterized by a reduction of endothelial anticoagulatory potential, favoring instead a procoagulatory milieu (McGorisk and Treasure, 1996). This shift enhances coronary thrombus formation in the case of fissured or ruptured plaque.

In summary, endothelial dysfunction is a systemic disorder that has a fundamental role in the development of atherosclerosis and its complications. Current evidence suggests that the integrity of the endothelium depends on the balance of all cardiovascular risk factors and vasculoprotective effects in a given individual, and endothelial dysfunction can be regarded as a marker of an inherent risk for atherosclerosis. In line with this hypothesis, the presence of endothelial dysfunction in either coronary or peripheral vessels has been shown to be an independent predictor for adverse cardiovascular outcomes providing prognostic information additional to that derived from conventional risk factor assessment (Frank *et al.*, 1990).

Endothelial glycocalyx in perioperative cardiac morbidity

Compared with an nonoperative setting, the role of endothelial dysfunction is much less investigated in perioperative cardiac morbidity. Major surgery predisposes to several factors that may damage the endothelium, including sympathoadrenal activation, systemic inflammation, ischemia-reperfusion, tissue injury, blood volume loss, and, on the other hand, hypervolemia due to extensive perioperative fluid management. Similarly to nonoperative myocardial ischemia and infarction, many of the risk factors for perioperative endothelial injury are congruent with those for perioperative cardiac complications. As discussed earlier, the current knowledge on pathophysiology of perioperative myocardial ischemia and infarction is mainly theoretical and based on diverse observations. Furthermore, the pathophysiology of PMI likely differs to some extent from that of nonoperative MI and the majority of perioperative MIs are of type 2 (Biccard and Rodseth, 2010). Findings from several animal models (Kurzelewski *et al.*, 2005; Mulivor and Lipowsky, 2004; Platts *et al.*, 2003; Wang *et al.*, 2005) and one observational study including aortic surgery patients (Rehm *et al.*, 2007) indicate that endothelial glycocalyx sheds during ischemia-reperfusion and major surgery, and this seems to be a trigger for postoperative edema, inflammation, and complications. Moreover, endothelial injury is known to impairs vasodilatation, contributes to enhanced plaque vulnerability and possible rupture, and favors thrombus formation (Bonetti *et al.* 2003). In the light of these observations, endothelial dysfunction appears to be a logical contributor to the development of perioperative myocardial ischemia and PMI. However, currently there are only a few studies that have been investigated perioperative endothelial glycocalyx injury in humans, and its potential association with PMI is unknown.

Rehm and colleagues in 2007 provided the first evidence for shedding of the endothelial glycocalyx in patients undergoing surgeries for thoracic and abdominal aorta. The authors demonstrated a multiple rise in syndecan-1 and heparan sulfate plasma levels after either global or regional ischemia followed by reperfusion. However, ICAM-1 and VCAM-1 levels remained

basically unchanged (Rehm *et al.*, 2007). The association of endothelial injury with postoperative complications was not investigated in this study. In 2014 Manchurov and colleagues reported the results of a small, albeit interesting clinical trial of the effect of remote ischemic preconditioning (RIPC) on endothelial function in patients with acute MI undergoing primary percutaneous coronary interventions (pPCIs) (Manchurov *et al.*, 2014). Endothelial function was assessed using the brachial artery flow-mediated dilation test (Thijssen *et al.*, 2011). The authors showed that RIPC significantly improved endothelial function and the effect remained constant up to the seventh day after the procedure. The improvement was speculated to be due to elevation of Nrf2, which may activate the genes responsible for anti-oxidation and detoxification in the endothelial cells (Cattaneo *et al.*, 2013; Purdom-Dickinson *et al.*, 2007). Despite the improved endothelial function in the RIPC group, the results of PCI as well as post-procedural cardiac functions were comparable between the two groups (Manchurov *et al.*, 2014). No other outcome measures were investigated in this study. Another study investigating endothelial injury in patients with acute MI undergoing PCI was published in 2013 by Ostrowski and colleagues (Ostrowski *et al.*, 2013). The authors investigated the potential association between sympathoadrenal activation and endothelial injury and the effect of these on adverse long-term outcomes (all-cause mortality, cardiovascular mortality, re-myocardial infarction, and heart failure requiring hospitalization). Endothelial injury was assessed with a single measurement of soluble thrombomodulin (sTM) and syndecan-1 at the beginning of pPCI. The results indicated that sympathoadrenal activation, reflected by high plasma levels of adrenalin and noradrenalin, correlated weakly but significantly with endothelial injury, and furthermore, adrenalin and syndecan-1 were associated with heart failure and mortality (Ostrowski *et al.*, 2013).

The data on endothelial dysfunction after (surgical) procedures and its association with adverse outcomes is scarce and rather low in quality. The markers and methods used to demonstrate endothelial injury vary largely between studies. Since the first description of endothelial dysfunction in atherosclerotic coronary arteries in 1986 by Ludmer and colleagues (Ludmer *et al.*, 1986), invasive assessment of coronary endothelial function by quantitative coronary angiography and Doppler flow measurements along with graded intracoronary infusions of endothelium-dependent vasodilators could be considered the "gold standard" for testing of endothelial function (Hasdai and Lerman, 1999). Since 1990s, however, less invasive or noninvasive techniques have been developed. These include strain gauge forearm plethysmography in conjunction with intra-arterial infusion of endothelium-dependent vasodilators and ultrasound measurement of flow-mediated endothelium-dependent dilatation (FMD) of the brachial artery during reactive hyperemia. The techniques are based on the understanding that endothelial dysfunction is not restricted to the coronary arteries, but is a systemic disorder that affects also peripheral vasculature. Indeed, FMD has

been shown to correlate with coronary dilatation by two studies (Anderson *et al.*, 1995; Takase *et al.*, 1998). However, despite efforts to standardize the use of FMD (Corretti et al., 2002), protocols still vary among different laboratories and are investigator-dependent (Corretti *et al.*, 2002; Anderson, 1999). Recent clinical studies have commonly used plasma levels of circulating endothelial glycocalyx components to detect endothelial injury (Rehm *et al.*, 2007; Ostrowski *et al.*, 2013; Bro-Jeppesen *et al.*, 2016; Johansen *et al.*, 2015; Ostrowski et al., 2015). Although it can be demonstrated that some of these components originate from the coronary glycocalyx, (Rehm et al., 2007), no study has shown in humans that detection of endothelial glycocalyx markers in peripheral circulation correlates with coronary endothelial injury. Furthermore, the superiority of any marker in demonstrating endothelial injury in clinical setting has not been demonstrated.

To summarize, considering the mechanisms of endothelial glycocalyx injury and physiological disturbances potentially associated with major surgery, it is hardly surprising to detect signs of endothelial dysfunction after surgery. Whether this has an impact on perioperative cardiac complications and postoperative survival needs to be confirmed by further investigations. Also unclear is whether preoperatively detected endothelial dysfunction could be an additional tool for perioperative cardiac risk stratification and whether interventions aimed at maintaining glycocalyx integrity prevent perioperative cardiac complications, opening the door for future studies.

ASSESSING PERIOPERATIVE CARDIAC RISK

Are intensified perioperative monitoring and cardiac enzyme follow-up recommended for all patients undergoing major non-cardiac surgery? Probably not. The risk for perioperative cardiac complications is only 1-2% in patients aged 40 years (Goldman, 1994) and, while not investigated, is likely even lower in younger patients. Instead of exposing patients to unnecessary examinations that sometimes require a significant amount of resources and are costly, we need to be able to identify the patients with increased cardiac risk and focus on this group in terms of intensified perioperative monitoring.

The medical history and clinical examination remain applicable and efficient primary methods to roughly differentiate patients with high and low perioperative cardiac risk. The risk is estimated to be increased in elderly patients with an underlying heart disease, especially if manifested by a recent myocardial infarction or heart failure (Goldman, 1994), in patients with PAD, especially if manifested by chronic limb-threatening ischemia, (McFalls *et al.*, 2008), in patients with chronic kidney disease (CKD), (Mooney *et al.*, 2014), or in patients with preoperatively elevated B-type natriuretic peptide (BNP) (Rodseth *et al.*, 2014). Furthermore, even preoperatively elevated cardiac troponin levels increase the risk for postoperative mortality (Maile *et al.*, 2016). International guidelines emphasize the importance of

assessing patients' cardiopulmonary fitness or functional capacity when determining the risk for perioperative morbidity and mortality (Kristensen *et al.*, 2014; Fleisher *et al.*, 2014). However, subjective assessment of functional capacity correlates poorly with validated methods, such as questionnaires and cardiopulmonary exercise testing, and has a poor accuracy when used to predict postoperative complications and mortality (Wijeysundera *et al.*, 2018).

To standardize and simplify cardiac risk stratification before non-cardiac surgery, several cardiac risk indices have been developed based on the forementioned and other risk factors. The first tool for cardiac risk prediction was developed as early as in 1977 by Goldman and colleagues (Goldman *et al.*, 1977), and since then other indices have followed based on either modification of Goldman's index or on new variables. Most of the indices estimate the perioperative risk based on the patient's preoperative condition and surgery-specific risk factors. However, in late 1980s and mid 1990s, Eagle and Vanzetto developed indices that combined clinical risk factors with dipyridamole-thallium imaging (Eagle *et al.*, 2002) and thallium – single-photon emission computed tomography (Vanzetto *et al.*, 1996). The authors demonstrated that the combination of clinical risk factors and cardiac imaging findings predicted perioperative cardiac complications better than either one alone. Based on the Eagle and Vanzetto criteria and Detsky's modified cardiac risk index (see Table 2), American College of Physicians (ACP) published guidelines for assessing and managing perioperative cardiac risk (Palda and Detsky, 1997). The guidelines included two steps: First, high-risk patients were identified using Detsky's index. The remaining patients were classified into low (0-1 clinical risk factors) and intermediate (> 2 clinical risk factors) risk groups based on the clinical risk factors by Eagle and Vanzetto. Second, the type of surgery was considered. Patients with low risk could proceed directly to surgery. For those with intermediate risk, no further testing was required if the surgery was non-vascular. Patients undergoing vascular surgery should undergo either dipyridamole-thallium imaging or dobutamine stress echocardiography. Those with a negative test could proceed to surgery and those with a positive test were placed into high-risk group. Patients with high cardiac risk should been subclassified based on the nature of risk: if the risk was primarily due to ischemic heart disease, coronary revascularization should be considered; if the risk was due to heart failure, valvular disease, or arrhythmia, medication should be optimized and risk should be reassessed; if the risk was due to non-modifiable factors, such as age, the surgery should be modified or cancelled. The ACP guidelines were initially a purely evidence-based recommendation for assessing and managing perioperative cardiac risk. However, today, the regularly updated American College of Cardiology/American Heart Association (ACC/AHA) guidelines have mostly replaced the ACP guidelines in routine clinical use, as the guidelines better reflect modern surgery and perioperative care.

Table 2 summarizes the different cardiac risk indices currently available, most recent ones of which are available as electronic calculators.

Table 2. *Cardiac risk indices.*

Index	N	Population	Outcome(s)	Predictors	Principle	Comments
Goldman's original CRI 1977	1001	Consecutive patients aged > 40 y undergoing major non-cardiac surgery (orthopaedic, urologic, general surgery)	Cardiac death, MI, pulmonary oedema, ventricular tachycardia	MI within 6 months, Age > 70, S3/jugular venous distention, significant aortic stenosis, non-sinus rhythm in last preoperative ECG, > 5 PVC/min in any preoperative ECG, poor general status*, intraperitoneal, intrathoracic or aortic surgery, emergency operation	3-11 points for each predictive condition. Based on the amount of points 4 risk classes are defined: I (0-5 points), 1% risk for cardiac complications; II (6-12 points), 7% risk for cardiac complications; III (13-25 points), 14% risk for cardiac complications; IV (≥ 26 points), 78% risk for cardiac complications	First large prospective multivariate analysis. Has been externally validated. Does not reflect today's medical and perioperative management
Detsky modified CRI 1986	455	Consecutive patients referred to preoperative evaluation prior to minor or major non-cardiac surgery	Cardiac death, MI, pulmonary oedema, ventricular tachycardia	MI within 6 months, MI within > 6 months, Age > 70, UAP, SAP, pulmonary oedema within 1 week or ever, significant aortic stenosis, non-sinus rhythm in last preoperative ECG, > 5 PVC/min in any preoperative ECG, poor general status, emergency intraperitoneal operation	5-20 points for each predictive condition. Based on the amount of points 4 risk classes are defined: I (0-5 points), 6% risk for cardiac complications; II (6-12 points), 7% risk for cardiac complications; III (13-25 points), 20% risk for cardiac complications; IV (26-100 points), 100% risk for cardiac complications	Derivation cohort included both minor and major surgeries and combined the risk of a specific surgery with the risk of an individual patient (based on existing predictive conditions)
Larsen risk index 1987	2609	Patients aged > 40 y undergoing elective non-cardiac surgery	Cardiac death, MI, pulmonary oedema, ventricular tachycardia	MI within 3 months, congestive heart failure, CAD, DM, serum creatinine > 139 umol/l, emergency operation, type of operation	2-12 points for each predictive condition. The total points define the estimated complication rate: 0 points, 0.3%; 5 points, 1.8%; 10 points, 9%; 15 points, 34%; 19 points, 66%; 25 points, 94%	In the derivation cohort, the SEs of some of the predictors were large and some insignificant variables were close to the level of significance (i.e. age > 60 y).

Table 2. *Cardiac risk indices.*

Lee RCRI 1999	4315 (2893/1422)[a]	Patients aged > 50 y undergoing elective non-cardiac surgery with LOS ≥ 2 days	MI, pulmonary oedema, ventricular fibrillation, cardiac arrest, complete heart block	High risk surgery (intraperitoneal, -thoracic, suprainguinal vascular surgery), CAD, heart failure, stroke/TIA, DM requiring insulin, preoperative serum creatinine > 177 umol/l	1 point for each predictive condition. Based on the amount of points 4 risk classes are defined: 0 points, 0.4-0.5% risk for cardiac complications; 1 point, 0.9-1.3% risk for cardiac complications; 2 points, 4.0-7.0% risk for cardiac complications; ≥ 3 points, 9.0-11.0% risk for cardiac complications	Simple to use. Has been externally validated and still widely in use. Lacking the ability to predict the risk of an individual patient and may underestimate the risk in vascular surgery
Gawande Surgical Apgar score 2007	1189 (311/103 and 775)[a]	Retrospective cohort. Patients aged > 16 y undergoing major general or vascular surgeries. Traumas, trans-plantations and minor operations excluded	Major complication within 30 days after surgery[δ]	Intraoperative lowest heart rate, estimated blood loss, lowest mean arterial blood pressure	Each predictor has 4 categories indicating the severity of the condition (i.e. estimated blood loss of > 1000ml, 601-1000ml, 101-600ml, ≤ 100ml). 0-4 points for each predictor based on the category a patient belongs to. Max 10 points. A lower total amount of points indicates a greater risk for major 30-day complications	Simple to use. Has been externally validated with consistent results. Does not specifically predict perioperative cardiac risk. Retrospective cohort
Bertges VSGNE 2010	10081 (8208/1873)[a]	Retrospective cohort. Patients undergoing elective CEA, OAAA, EVAR, and LEB surgeries	The composite of in-hospital MI, heart failure or clinically significant new cardiac arrhythmia	Increasing age (60-69, 70-79, ≥ 80), CAD, heart failure, COPD, smoking, serum creatinine > 159 umol/l, DM requiring insulin, long-term β-blockade, coronary revascularization (PCI/CABG), non-invasive cardiac stress test result[¶]	-1-4 points for each predictive condition. Based on the amount of points 6 risk classes are defined: 0-3 points, 2.6% risk for cardiac complications; 4 points, 3.5% risk for cardiac complications; 5 points, 6% risk for cardiac complications; 6 points, 6.6% risk for cardiac complications; 7 points, 8.9% risk for cardiac complications; ≥ 8 points, 14.3% risk for cardiac complications	Compared to Lee RCRI, predicts better the risk in vascular surgery. Lacking external validation. Retrospective cohort

Table 2. *Cardiac risk indices.*

Gupta Calculator 2011	(211 410/ 257 385)[a]	Retrospective cohort from the American College of Surgeons' NSQIP database. Patients undergoing elective/ urgent non-cardiac and cardiac surgeries	MI, cardiac arrest	Increasing age, ASA class, dependent functional status, serum creatinine > 133 umol/l, type of surgery	A multivariate logistic regression-derived combination of risk factors predictive for MI or cardiac arrest. Based on the original analysis each predictor or a combination of predictors give an actual number for a risk of MI or cardiac arrest after surgery. The calculator is available at www.surgicalriskcalculator.com/ miorcardiacarrest	Simple to use. Large derivation and validation cohort. Lacking external validation. Retrospective cohort
Davis R-RCRI 2013	9591	Retrospective cohort from the CAIS database. Patients aged > 50 y undergoing elective non-cardiac surgery with LOS ≥ 2 days	MI, pulmonary oedema, cardiac arrest	High risk surgery (intraperitoneal, -thoracic, suprainguinal vascular surgery), CAD, heart failure, stroke/TIA, preoperative GFR < 30mL/min	Developed to test, whether a different categorization of preoperative renal function and DM affect the predictive accuracy of the RCRI. Despite re-categorization, DM did not improve the accuracy of the index, but GFR < 30mL/min did and was included in the R-RCRI. The use of the index is similar to Lee RCRI	Simple to use. Lacking external validation. Retrospective cohort; varying clinical practices may have been affected on the reporting of outcomes
Bilimoria American College of Surgeons' NSQIP surgical risk calculator 2013	141 4006	Retrospective cohort from the American College of Surgeons' NSQIP database. Patients undergoing elective/ urgent non-cardiac and cardiac surgeries	Mortality, pneumonia, MI or cardiac arrest, surgical site infection, urinary tract infection, deep venous thrombosis, renal failure, morbidity[‡]	20 different variables§ covering demographics and medical history, CPT-specific risk and a subjective surgeon adjustment score, which allows surgeons to modify the estimated risk based on their impression of the patient	A web-based tool that calculates the risk of an individual patient (separately for each outcome) using specific regression models and compares it to the average risk. The surgeon adjustment score allows clinicians to increase the risk of surgery within the confidence interval for the predicted risk. The calculator is available at http://riskcalculator.facs.org/RiskCalculator/	Externally validated. Because of varying numbers of subspecialties in the derivation cohort, performs somewhat unevenly in predicting complications in different subspecialties. Retrospective cohort

Table 2. *Cardiac risk indices.*

* PO2 < 60 mmHg; PCO2 > 50 mmHg; K < 3.0 mmol/l; HCO 3 < 20 mmol/l; blood urea nitrogen > 18 mmol/l; creatinine > 260 umol/l; abnormal SGOT; signs of chronic liver disease; bedridden from non-cardiac causes.

[a] Derivation cohort/validation cohort

[δ] Death, AKI, bleeding requiring ≥ 4 U red blood cell transfusion within 72 hours after operation, cardiac arrest requiring CPR, coma for 24 hours or longer, deep venous thrombosis, septic shock, MI, unplanned intubation, ventilator use for 48 hours or longer, pneumonia, pulmonary embolism, stroke, wound disruption, deep or organ-space surgical site infection, sepsis, systemic inflammatory response syndrome, vascular graft failure.

[¶] Was later removed from the model to provide a purely clinical index.

[‡] Any of the afore-mentioned or wound disruption, unplanned intubation, pulmonary embolism, ventilator dependency > 48h, stroke/TIA or systemic sepsis

[§] Age (< 65; 65-74; 75-84; ≥ 85 years), sex, functional status, emergency surgery, ASA class, steroid use, ascites within 30 days preoperatively, system sepsis within 48 hours preoperatively, ventilator dependency, disseminated cancer, DM, hypertension requiring medication, previous cardiac event, CHF within 30 days preoperatively, dyspnoea, current smoker (within 1 year), history of COPD, dialysis, AKI, body mass index class.

Abbreviations: CRI, cardiac risk index; MI, myocardial infarction; ECG, electrocardiogram; PVC, premature ventricular complex; UAP, unstable angina pectoris; SAP, stable angina pectoris; CAD, coronary artery disease; DM, diabetes mellitus; SE, standard error; RCRI, revised cardiac risk index; LOS, length of stay; TIA, transient ischemic attack; VSGNE, vascular study group of New England; CEA, carotid endarterectomy; OAAA, open abdominal aortic aneurysm repair; EVAR, endovascular abdominal aortic aneurysm repair; LEB, lower extremity bypass; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; NSQIP, national surgical quality improvement program; ASA, American society of anesthesiologists; R-RCRI, reconstructed revised cardiac risk index; CAIS, clinical anesthesia information system; CPT, current procedural terminology; AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; CHF, congestive heart failure.

In contrast to other indices, the surgical Apgar score includes only intraoperative variables (Gawande *et al.*, 2007). Furthermore, the surgical Apgar score does not give a specific numerical risk for certain perioperative complications, but rather helps to identify the patients who warrant more intensive monitoring. The Revised Cardiac Risk Index (RCRI), or Lee's index (Lee *et al.*, 1999), is the most widely spread and commonly used index for predicting major cardiac complications today. It has some limitations, however, including a relatively weak ability to predict an individual patient's absolute cardiac risk. Furthermore, some components of the index should be revised to better suit modern surgery and perioperative care (Sankar *et al.*, 2015). In attempting to overcome the shortages of RCRI, new indices have been developed, one of which is the Gupta cardiac risk calculator (Gupta *et al.*, 2011). This index was developed using the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) 2007's database including over 200 000 patients and validated a year later with a similarly sized cohort. Compared with RCRI, the index has been shown to be more

accurate in predicting major cardiac complications (Gupta *et al.*, 2011), and the authors have modified the index to predict specific complications in subspecialties of vascular surgery (Gupta *et al.*, 2012; Gupta *et al.*, 2013). However, these indices lack validation outside the United States and are somewhat limited by the manner in which the NSQIP registry ascertained the relevant outcomes, i.e. all the participating sites did not apply postoperative troponin surveillance (Bilimoria *et al.*, 2013), and this has been likely led to significant underreporting of PMI rates.

Additional clinical tests might be preoperatively performed to acquire more accurate information about a patient's underlying heart disease or functional capacity. These tests may be of most value in patients with moderate perioperative cardiac risk, especially considering the questionable accuracy of subjective assessment of functional capacity (Wijeysundera *et al.*, 2018). The noninvasive tests most commonly performed today include resting echocardiogram, cardiac stress test, and cardiopulmonary exercise testing (CPET). Although all of these tests provide comprehensive information on the patient's cardiopulmonary condition, evidence on whether this information is beneficial regarding the postoperative survival is scarce and conflicting, with the exception of cardiac stress testing (Augoustides *et al.*, 2013). Resting echocardiogram provides information on potentially prognostic ventricular systolic and diastolic function, valvular abnormalities, wall motion abnormalities, and pulmonary hypertension. The available data indicate that preoperative systolic dysfunction is associated with a higher risk for perioperative cardiac complications and death (Rohde *et al.*, 2001). However, confirming this with echocardiogram may not improve risk prediction beyond routine clinical examination (Rohde *et al.*, 2001). Furthermore, resting echocardiogram is not a proxy measure of functional capacity in individuals who cannot exercise, for example, because of obesity or arthritis (Franciosa *et al.*, 1981). Cardiac stress testing seems to add predictive value and is beneficial regarding postoperative survival in patients with intermediate or high cardiac risk (Augoustides *et al.*, 2013). Obviously, patients need to be physically able to perform the test. If cardiac stress test is performed, the ability to reach at least seven metabolic equivalents of task (METs) is indicative of low perioperative cardiac risk, whereas a failure to reach four METs indicates increased risk (Sgura *et al.*, 2000). Moreover, in the case of cardiac stress imaging, reversible defects indicate increased perioperative cardiac risk, with greater extent of reversibility being associated with progressively increasing risk (Etchelles *et al.*, 2002). By contrast, isolated fixed defects are not indicative of increased perioperative cardiac risk (Etchelles *et al.*, 2002). CPET is an increasingly popular method for perioperative risk assessment (Huddart *et al.*, 2013). The test provides an objective measure of cardiopulmonary fitness, and besides cardiac events, (Wijeysundera *et al.*, 2018), predicts a range of perioperative complications such as pneumonia, respiratory failure, and infection (Sankar *et al.*, 2015). CPET-derived measurements indicative of perioperative morbidity and

mortality include inability to exercise at all, low anaerobic threshold (<11ml/kg/min), and low peak oxygen uptake (Wijeysundera et al., 2018; James *et al.*, 2014; Raby *et al.*, 1989). However, these findings need to be confirmed in larger studies that include multiple sites and heterogeneous generalizable cohorts. In addition to the above-mentioned methods, ischemic changes in ambulatory ECG monitoring have been shown to predict perioperative cardiac complications and mortality (Frank *et al.*, 1990; Ganz *et al.*, 1994; Landesberg *et al.*, 1993; Raby *et al.*, 1989). Nonetheless, this monitoring method is today seldom applied in perioperative risk assessment, probably due to the amount of resources required. Rapid developments are occurring in light and in some cases wireless, patient-monitoring devices, and ambulatory ECG monitoring, as well as monitoring of other of other vital parameters, thus, these monitoring methods will likely establish itself again in perioperative research and care.

In addition to noninvasive tests, the value of preoperative coronary angiography in predicting perioperative cardiac complications has been investigated (Hwang et al., 2015; Sheth *et al.*, 2015). Although coronary angiography adds prognostic information to clinical risk assessment (Hwang *et al.*, 2015; Sheth *et al.*., 2015), it more commonly overestimates the risk in patients who will not suffer a perioperative cardiac complication. Overestimation of the cardiac risk can have negative consequences. It can lead to unnecessary declining or delaying of surgery or even prophylactic coronary revascularization, which is not risk-free and is of uncertain value in the perioperative period (McFalls *et al.*, 2004).

There is a limited amount of resources to monitor the highest risk patients after surgery. Intensive monitoring and restriction of mobilization can be harmful to the patients who do not actually need it, and this misallocates the resources from the patients who genuinely are at high risk. Moreover, the findings of coronary angiography can sometimes be in conflict with the clinical outcome. For example, a prospective study by Seth *et al.* (2015) showed that 28% of the patients who sustained PMI had only minor or no coronary stenoses, and, on the other hand, of the six patients with suspected left main stenosis who underwent a surgery, none suffered PMI (Sheth *et al.*, 2015). Thus, preoperative coronary angiography is not recommended unless it would be performed independently of surgery (Pannell *et al.*, 2013). However, routine cardiology consultation and individual preoperative optimization prior to elective surgery may be beneficial, as recently shown by Squizzato *et al.* (2020). Routine preoperative cardiology consultation should be considered for patients with moderate to high cardiac risk.

PREVENTIVE STRATEGIES FOR PERIOPERATIVE CARDIAC COMPLICATIONS

Prevention of perioperative cardiac complications has been extensively studied during the last decades. However, we still have only a few firm recommendations regarding perioperative cardiac protection, and today's guidelines are mostly able to tell us what not to do instead of offering specific preventive strategies.

In terms of perioperative medication, the results of the trials have mostly been disappointing. Optimization of medical therapy seems beneficial, especially in patients with cardiovascular risk factors (*et al.*, 2014). The problem is, however, that in the current practice most patients are not seen weeks but rather only days before surgery, and it is usually too late to start to and titrate new medications. Furthermore, postponing the surgery is not always possible.

Smoking cessation

Smoking is a well-recognized risk factor for cardiovascular morbidity. Cigarette smoke damages the endothelial glycocalyx, leading to a reduced prostacyclin production, increased platelet adhesion, and development of atherosclerotic lesions (Pittilo, 2000). However, the effect of smoking status on perioperative cardiac complications has been investigated seldom. In 2014, a systematic review and meta-analysis including 107 studies showed that preoperative smoking was associated with increased general postoperative morbidity, wound complications, general infections, pulmonary complications, neurological complications, and admission to intensive care unit. However, no differences emerged between smokers and non-smokers in postoperative mortality, cardiovascular complications, bleeding, anastomotic leakage, or allograft rejection (Grønkjær *et al.*, 2014). Recently, Arinze and colleagues investigated the effect of the duration of perioperative smoking cessation in a large retrospective study of patients undergoing major elective vascular surgery. There were no differences between the effect of long-term smoking cessation, short-term smoking cessation, and current smoking on perioperative myocardial infarction or mortality. However, long-term smoking cessation was associated with fewer pulmonary complications in patients undergoing open abdominal aortic aneurysm repair (Arinze *et al.*, 2019).

Beta blockers

Despite initially promising research results (Feringa *et al.*, 2006; London *et al.*, 2013; Raby *et al.*, 1999; Welten *et al.*, 2007) and previous widespread use for cardiac protection, de novo administration of beta blockers is highly controversial today. A recent meta-analysis demonstrated that beta blockers started within a day or less before surgery decreased the incidence of PMI, but at a cost of higher rates of stroke and death (Wijeysundera et al., 2014). However, a recent retrospective study by Friedell *et al.* (2015) showed that patients with high cardiovascular risk had a lower 30-day postoperative mortality if receiving beta blockers. Beta blocker had no effect on the mortality of the patients with intermediate risk and were harmful to patients with no cardiovascular risk factors (Friedell *et al.*, 2015). However, in approximately half of the patients, beta blockers were not started de novo, which might explain the results. Dose titration, as recommended in the current ACC/AHA guidelines, may optimize beta blockade, thus decreasing the undesired effects, namely bradycardia and hypotension, of the treatment (Anderson *et al.*, 2007; Antman *et al.*, 2008). Furthermore, the choice of beta blocker likely matters. The metabolism of metoprolol succinate, used, for example, in the POISE trial, (Devereaux *et al.*, 2008), may lead to significant differences in metoprolol plasma concentrations between individual patients (Ismail and Teh, 2006). Contrary to an oral fixed-dose regimen, intravenous short-acting betablockade targeting prespecified heart rate and blood pressure levels might be promising in reducing perioperative myocardial ischemia without predisposing vital organs to hypoperfusion. One previous meta-analysis investigated this subject ten years ago and showed that esmolol reduced perioperative myocardial ischemia without adverse side-effects (Landoni *et al.*, 2010). Patient-centered clinically significant outcomes, such as mortality, were not investigated, and data regarding perioperative intravenous beta blockade are scarce.

Currently, the European and American guidelines suggest the perioperative continuation of beta blockers in those patients already on medication (Class I, Level B). The preoperative initiation of beta blockers may be considered for patients with high perioperative cardiac risk undergoing high-risk surgery (Class IIb, Level B), however, not without preoperative titration (Class III, Level B) (Kristensen *et al.*, 2014; Fleisher *et al.*, 2014).

Aspirin, other antiplatelets, and anticoagulants

Perioperatively started aspirin medication does not decrease PMI or mortality, even in patients with cardiovascular risk factors, but instead increases the risk for perioperative bleeding (Devereaux *et al.*, 2014).

By contrast, dabigatran at a dose of 110 mg twice daily reduced the composite of vascular mortality, non-fatal myocardial infarction, non-

hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism during the 16-month follow-up of patients who sustained MINS, without a significant increase in major bleeding, in the recent MANAGE study (Devereaux *et al.*, 2018). It is important to note, however, that the definition of major bleeding in MANAGE was such that many patients with significant bleeding problems, even requiring transfusions, did not meet the definition (Adriaenssens and Sinnaeve, 2018). There were no differences in secondary outcome measures, i.e. all-cause mortality and myocardial infarction, between the dabigatran and placebo groups. Over half of the patients used concomitant medications, such as aspirin, statins, or beta blockers, during the follow-up. However, the groups did not differ in terms of concomitant medication use (Devereaux *et al.*, 2018).

A subgroup of surgical patients who seem to benefit from perioperative antiplatelet and anticoagulant treatment are patients with PAD. Recently, thrombin inhibition with a low-dose factor Xa inhibitor added to antiplatelet therapy has been demonstrated to be beneficial in preventing cardiovascular events and mortality in patients with systemic atherosclerosis. The COMPASS study showed that low-dose rivaroxaban (2.5 mg twice daily) combined with aspirin (100 mg once daily) significantly reduced the combined primary outcome of stroke, cardiovascular death, and myocardial infarction in patients with peripheral artery disease and stable CAD. Furthermore, dual pathway inhibition reduced major adverse limb events by 46% (Eikelboom *et al.*, 2017; Steffel *et al.*, 2020). The need for peripheral revascularization identifies a subgroup of patients with PAD at the highest risk of cardiovascular events. The VOYAGER PAD study was initiated to evaluate the efficacy and safety of low-dose rivaroxaban used together with aspirin in patients with PAD undergoing lower extremity revascularization. The results of this large, double-blind randomized controlled trial demonstrated that dual pathway inhibition significantly reduced the combined primary outcome of acute limb ischemia, major amputation of vascular etiology, MI, stroke, and cardiovascular death, compared with aspirin alone. Kaplan-Meier event estimates demonstrated the benefit of dual pathway inhibition already three months after the initiation of the treatment and the benefit increased over the entire follow-up (Bonaca *et al.*, 2020). Although the benefit of rivaroxaban and aspirin following lower extremity revascularization appeared to be mainly due to a reduction in acute limb ischemia, treatment reduced hospitalization for coronary or peripheral thrombotic events as well. There were no differences in all-cause mortality between the two groups. In both the COMPASS study and the VOYAGER PAD study, patients with dual pathway inhibition had more bleeding than patients with aspirin monotherapy. In the COMPASS study, the difference was statistically significant, although intracranial and fatal bleeding rates were low overall and did not show a significant excess with rivaroxaban. In the VOYAGER PAD study, major bleeding rates were 2.65% with rivaroxaban-aspirin combination and 1.87% with aspirin monotherapy ($p=0.07$). There were no statistically significant differences in fatal bleeding

rates between the groups. Whether antiplatelets or anticoagulants become a routine management of perioperative cardiac complications depends on future studies and analyses.

Currently, the ACC/AHA guidelines state that continuation of aspirin in the case of nonurgent, non-cardiac surgery may be reasonable in patients without prior coronary stenting if the risk for perioperative cardiac complications outweighs the risk for bleeding (Class IIb, Level B) (Fleisher *et al.*, 2014). In the case of patients with recent coronary stenting undergoing urgent surgery, antiplatelets should be continued, and if not possible, restarted as soon as possible after the surgery (Class I, Level C) (Fleisher *et al.*, 2014).

α-2 agonists and antihypertensive agents

α-2 agonist clonidine might be efficient in reducing perioperative sympathetic activation and myocardial stress and its effect on cardiac protection was investigated in the POISE-2 trial (Devereaux *et al.*, 2014). Clonidine did not reduce the incidence of PMI, but did increase clinically significant hypotension and non-fatal cardiac arrest. α-2 agonists are not recommended for perioperative cardiac protection by either European or American guidelines (Class III, Level B) (Kristensen *et al.*, 2014; Fleisher *et al.*, 2014). The safety of prescribing angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on the day of surgery is unclear. Only few studies have investigated the effect of continuation or discontinuation of ACEIs and ARBs on the day of surgery, with the result that continuing renin-angiotensin system inhibition increased the risk of intraoperative hypotension (Rosenman *et al.*, 2008; Turan *et al.*, 2012; Roshanov *et al.*, 2017) and potentially increased the risk of MINS, stroke, and mortality at 30 days (Roshanov *et al.*, 2017). The (ESC/ESA) guidelines recommend considering temporary discontinuation of ACIs and ARBs prior to surgery when prescribed for hypertension, but recommend continuation in stable patients with heart failure or left ventricular dysfunction (Class IIa, Level C) (Kristensen *et al.*, 2014). The ACC/AHA guidelines indicate that ACI and ARB therapy should be continued over the perioperative period (Class IIa, Level B), and if the agents are discontinued, they should be restarted as soon as possible after the surgery (Class IIa, Level C) (Fleisher *et al.*, 2014). Data regarding perioperative calcium channel blockers are scarce. A meta-analysis from 2003 showed that calcium channel blockers reduced myocardial ischemia and supraventricular tachycardia, the majority of benefits being attributable to diltiazem (Wijeysundera and Beattie, 2003). Generally, calcium channel blockers are continued over the perioperative period for patients already on medication. There are no recommendations regarding initiation of calcium channel blockers only for perioperative cardiac protection.

Statins

In surgical patients, statins have been shown to reduce perioperative major cardiac complications and mortality. The effect has been shown in both large observational studies (Berwanger *et al.*, 2016; Lindenauer *et al.*, 2004; Suckow *et al.*, 2015) and randomized trials (Durazzo *et al.*, 2004; Xia *et al.*, 2015). In the recent observational study of the VISION cohort, perioperative statin use reduced the incidence of perioperative myocardial injury, reflected by troponin leakage during the first three postoperative days, in addition to 30-day mortality, MINS, and stroke (Berwanger *et al.*, 2016). The ACC/AHA guidelines recommend perioperative continuation of statin use (Class I, Level B). Initiation of statin therapy may be reasonable in patients undergoing vascular surgery (Class IIa, Level B) as well as in patients undergoing other high-risk surgeries with cardiovascular risk factors (Class IIb, Level C) (Fleisher *et al.*, 2014). However, the (ESC/ESA) guidelines suggest that for statin-naïve patients the treatment should be started two weeks before surgery (Kristensen *et al.*, 2014).

Coronary revascularization

Preoperative coronary revascularization does not improve long-term survival or prevent PMI or in-hospital death in patients with stable coronary artery disease (McFalls *et al.*, 2004). Thus, coronary revascularization should not be preoperatively performed, unless indicated independently of surgery (Class I, Level C) (Fleisher *et al.*, 2014). Regarding patients with recent coronary revascularization procedures, elective non-cardiac surgery should be delayed at least 14 days after balloon angioplasty, 30 days after implementation of bare-metal stent (BMS), and ideally 365 days after implementation of drug-eluting stent (DES) (Class I, Levels C and B) (Fleisher *et al.*, 2014).

Early coronary angiography after MINS was investigated in a recent observational study by Rostagno *et al.* (2019). The major limitation of the study was the small number of patients (only 20% of 92 patients with MINS underwent coronary angiography) and the selection bias; however, the study showed that early coronary revascularization might improve long-term survival after MINS (Rostagno *et al.*, 2019). Parashar *et al.* (2016) investigated the angiographic findings and short- and long-term survival in PMI patients admitted to coronary angiography with a focus on pPCI. The study did not compare the survival of PMI patients who did and did not undergo the procedure; however, the authors demonstrated that bleeding after PCI predicted both short- and long-term mortality. Other predictors were peak troponin level and PAD for short-term mortality and older age, vascular surgery, and renal dysfunction for long-term mortality (Parashar *et al.*, 2016).

Intraoperative and postoperative factors

Although volatile anesthetics have cardioprotective effects (Pagel, 2013), the use of volatile anesthetics has not reduced myocardial ischemia, major cardiac complications, troponin, or BNP concentrations in major non-cardiac surgery (Lindholm *et al.*, 2013; Lurati Buse *et al.*, 2012). Furthermore, as recently demonstrated by Landoni *et al.* (2019) and colleagues, volatile anesthetics do not reduce mortality among patients undergoing elective coronary artery bypass graft surgery. However, sevoflurane may reduce the need for inotropic support (Lindholm *et al.*, 2013). The potential benefits of neuraxial (epidural or spinal) anesthesia over general anesthesia have been highly debated in the literature. Studies, including randomized controlled trials and a meta-analysis, have shown some evidence of improved outcome and reduced postoperative morbidity with regional anesthesia (Bode *et al.*, 1996; Mauermann *et al.* 2006; Rigg *et al.*, 2002).A more recent retrospective analysis of nearly 400 000 patients undergoing total hip or knee arthroplasty observed a significant reduction in postoperative morbidity and mortality in patients receiving neuraxial anesthesia (Memtsoudis *et al.*, 2013). Currently, there are no studies investigating the effect of general versus neuraxial anesthesia targeting specifically patients with CAD. However, one meta-analysis investigated this effect in patients undergoing lower extremity revascularization – a subgroup of surgical patients at high risk of perioperative cardiac events. No differences were observed in mortality, myocardial infarction, or lower limb amputation between patients receiving neuraxial anesthesia and general anesthesia. Nevertheless, neuraxial anesthesia was associated with a significantly lower risk of postoperative pneumonia (Barbosa *et al.* 2013). Neuraxial anesthesia may be considered in patients with cardiac risk factors who do not have contraindications, such as antiplatelet or anticoagulant treatment, but the evidence of benefits is currently insufficient (Class IIb, Level B) (Kristensen *et al.*, 2014).

Blood loss and anemia are associated with impaired oxygen delivery to the tissues. Considering this, more liberal red blood cell transfusion thresholds after surgery might be beneficial in preventing perioperative cardiac complications and mortality. However, higher transfusion thresholds have not been shown to affect short- or long-term mortality in large trials (Carson *et al.*, 2011; Carson *et al.*, 2015). Regarding perioperative morbidity, liberal transfusion thresholds may indeed reduce myocardial infarction, but tend to increase other complications such as infections (Brunskill *et al.*, 2015). Overall, data regarding perioperative red blood cell transfusion thresholds for perioperative cardiac protection are limited, and no recommendations for optimal hemoglobin level exist. It is also possible that different patient groups benefit from different transfusion thresholds. A recent small study by Möller and colleagues suggested potential harm for patients undergoing major vascular surgery with restrictive transfusion thresholds (Möller *et al.*, 2019). Currently, further trials comparing liberal versus restrictive transfusion

thresholds are underway, and results can be expected in becoming years.

Blood pressure optimization seems to be beneficial. The association between intraoperative hypotension and mortality has been demonstrated in several observational studies (Abbott *et al.*, 2018; Monk *et al.*, 2015; Roshanov *et al.*, 2019; van Waes *et al.*, 2016; Walsh *et al.*, 2013). Furthermore, even short periods of intraoperative hypotension are associated with myocardial injury (Abbott *et al.*, 2018; Roshanov *et al.*, 2019; Walsh *et al.*, 2013). Recently, Roshanov and colleagues investigated the potential interaction between existing coronary artery disease and perioperative hypotension and demonstrated that perioperative hypotension is associated with 30-day myocardial infarction and cardiovascular mortality independently of the degree of CAD on perioperative coronary angiography (Roshanov *et al.*, 2019). Another recent study by Abbot and colleagues expanded on the current knowledge regarding perioperative hemodynamics and cardiac complications by demonstrating that in addition to intraoperative hypotension, also intraoperative tachycardia is associated with myocardial injury, myocardial infarction, and mortality (Abbott *et al.*, 2018).

Severe postoperative pain is reported in 5-10% of surgical patients. This increases sympathetic drive and delays recovery (Liu and Wu, 2007; White and Kehlet, 2007). Sympathetic activation increases myocardial oxygen consumption and may precipitate myocardial ischemia, especially if other risk factors are present. Therefore, efficient and patient-centered management of postoperative pain is essential. A meta-analysis published in 2013 compared the effects of epidural analgesia and systemic analgesia and showed that epidural analgesia was associated with a decrease in mortality, supraventricular tachyarrhythmias, deep-vein thrombosis, respiratory problems and pneumonia, and postoperative nausea, vomiting, and ileus (Pöpping *et al.*, 2013). Furthermore, in recent years, ultrasound-guided regional anesthetic techniques have developed, and especially different fascial plane blocks have become popular in truncal analgesia. These techniques provide a feasible alternative to thoracic epidural, for example, in patients with coagulation abnormalities and at increased risk of epidural hematoma. There is moderate evidence that fascial plane blocks and epidural analgesia are equally effective in treating postoperative pain, while fascial plane blocks are associated with fewer episodes of hypotension (Khalil *et al.*, 2017; Baeriswyl *et al.*, 2018). However, further investigation is needed to determine the safety and efficacy of these techniques for clinically relevant outcomes.

Finally, considering the significant effect of hemodynamic disturbances on perioperative cardiac complications, more frequent or continuous monitoring of vital signs and parameters has been proposed. A large meta-analysis by Maharaj and colleagues demonstrated that rapid response systems (RRS) are able to reduce in-hospital mortality and cardiopulmonary arrests, despite varying practices in vital sign monitoring and alarm activation (Maharaj *et al.*, 2015). However, opposing results have been presented as well (Chan *et al.*, 2010). Despite the compelling logic of frequent monitoring and timely delivery

of interventions, high-quality data showing an improvement in clinically significant patient-centered outcomes through monitoring are inconclusive at best. Furthermore, currently there are no high-quality studies focusing specifically on perioperative monitoring and its effect on perioperative cardiac complications.

AIMS OF THE STUDY

The purpose of this study was to investigate the incidence and prognosis of PMI in an unselected cohort of patients undergoing non-cardiac surgery in a Finnish tertiary care hospital and to evaluate how the Gupta cardiac risk calculator performs in predicting major perioperative cardiac complications outside the United States. Furthermore, this study aimed to examine the pathophysiological mechanisms of PMI by investigating the clinical significance of silent postoperative ischemia and perioperative glycocalyx injury. Finally, considering the pathophysiological mechanisms of PMI and hemodynamic factors affecting the development of perioperative myocardial ischemia, this study assessed whether intravenous esmolol would be efficient and safe in perioperative cardiac protection.

Specific aims of the study were as follows:

1. To investigate the incidence, prognosis and risk factors of PMI in an unselected cohort of patients undergoing non-cardiac surgery in a Finnish tertiary care hospital and to determine how the Gupta cardiac risk calculator performs in predicting major perioperative cardiac complications outside the United States (I).

2. To evaluate the incidence and clinical significance of silent postoperative myocardial ischemia in patients with high perioperative cardiac risk (II).

3. To examine the potential association of endothelial glycocalyx injury and systemic inflammation with development of PMI (III).

4. To determine whether intravenous esmolol, titrated according to prespecified heart rate and blood pressure levels, would be efficient and safe in perioperative cardiac protection (IV).

MATERIAL AND METHODS

This thesis comprises four different studies. Studies I-III are prospective observational studies, including adult non-cardiac surgery patients with systematic perioperative ischemia screening. Study IV is a systematic review of the literature and meta-analysis of the efficacy and safety of perioperative esmolol in preventing perioperative cardiac complications.

The results of Studies I-III are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (von Elm *et al.*, 2014). Briefly, this is an initiative developed to improve the reporting of results of observational studies. The guidelines aims to add transparency to observational studies and to enable critical assessment of the results by others. Furthermore, transparent reporting is needed to determine whether and how the results of an observational study can be included in systematic reviews. The STROBE guidelines consist of a 22-item check list that is presented in Appendix 1. The items cover the article's title and abstract (1), introduction (2-3), methods (4-12), results (13-17), discussion sections (18-21), and other information (22).

MATERIAL

Table 3 summarizes the patient cohorts and recruitment times of Studies I-III.

Table 3. *Summary of the patient flow of the studies I-III..*

	Recruitment period	Patients eligible for the study	Patients not enrolled in the study	Patients excluded from the final analysis	Patients in the final study cohort
Study I	April – June 2014	570	185 • 10 did not consent • 47 were unable to consent due to: - cognitive impairment (23) - morbid condition (20) - lack of common language (4) • 128 were not recruited due to: - urgent/emergency operation (82) - miscellaneous reasons (46)		560 • 385 with systematic ischemia monitoring • 175 with standard perioperative care
Study II	March – July 2015	90	33 • 2 did not consent 12 with pre-existing conduction defects in ECG • 19 were not recruited due to miscellaneous reasons	6 • 1 with bifascicular block and QRS > 200 ms • 1 with LBBB • 1 received digitalis • 1 with an electronic pacemaker • 2 with unanalysable cECG recordings	51
Study III	April – June 2014	385 • 27 with PMI • 358 without PMI	12 with PMI • 1 with all samples lost during storage • 4 with missing 6h samples • 2 with missing 24h samples • 5 with missing EDTA plasma samples • 298 without PMI		75 • 15 with PMI • 60 propensity matched

Abbreviations: ECG, electrocardiogram; LBBB, left bundle branch block; cECG, continuous electrocardiographic monitoring; PMI, perioperative myocardial infarction.

The selection process of the studies for the systematic review and meta-analysis (Study IV) is presented in Figure 4.

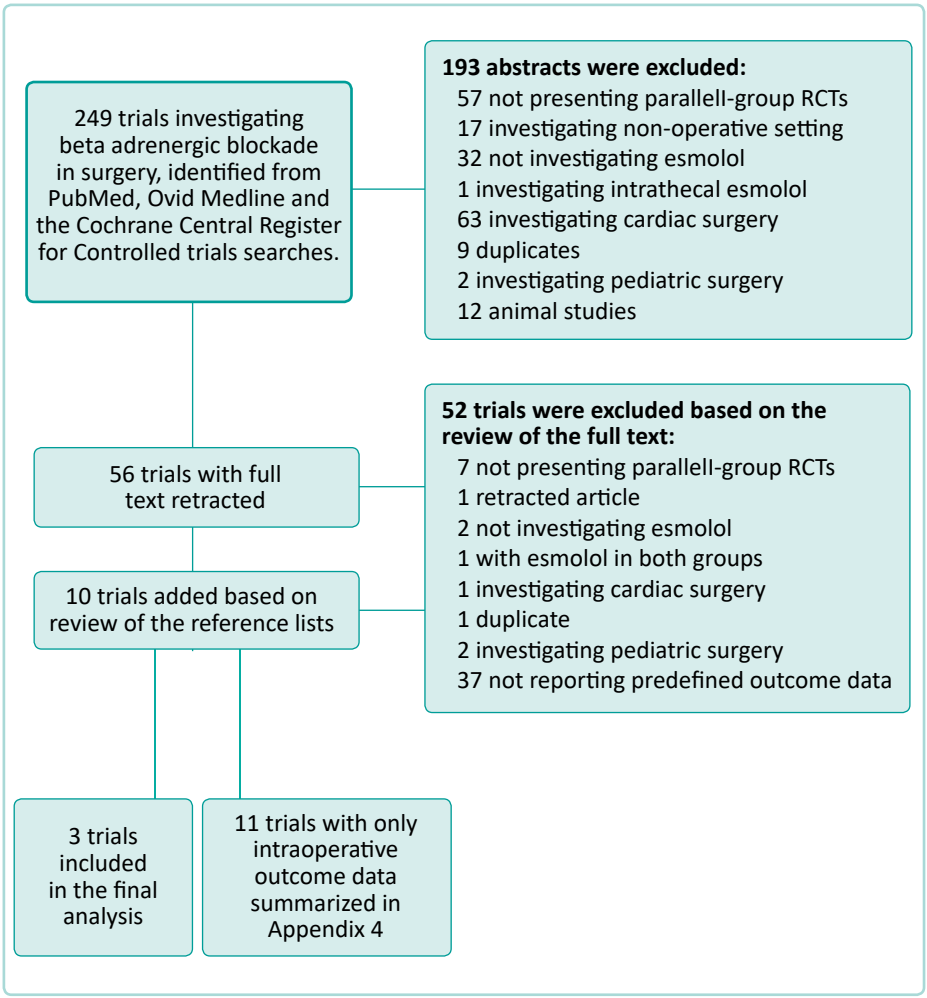

Figure 4. *The study selection process for the systematic review and meta-analysis (IV). RCT, randomized controlled trial.*

Considering the reported incidence of PMI in the earlier studies and in order to achieve a desirable width of confidence interval (CI), the aim was to recruit 500 consecutive patients in Study I. To ensure representativeness of the cohort, an amendment was applied to analyze the routine clinical data of the eligible patients whose consent was missing, mainly due to challenges during off-hour urgent operations. The recruitment took place between April and June 2014. All consecutive patients aged 50 years or older undergoing non-cardiac, non-organ transplantation surgery were considered eligible for the study.

In Study II, the aim was recruit patients at heightened risk for perioperative cardiac complications. The recruitment took place between March and July 2015. Patients aged 65 years or older undergoing vascular surgery were deemed eligible for the study. Both elective and urgent/emergency operations were included; however, recruitment took place only during office hours. The following patients were prospectively excluded: (1) those scheduled for a re-operation during the same hospitalization, (2) those assigned for treatment in the ICU after surgery, (3) those whose preoperative ECG included conduction defect precluding ST-segment analysis, and (4) those on digitalis medication.

The aims of Study III were to expand on the findings of Study I, and to investigate the potential association of endothelial glycocalyx injury with PMI. The patients included in Study I were investigated. All the PMI patients of the primary cohort with a complete series of follow-up blood samples (n=15) and four propensity-matched controls for each PMI patient (n=60) were included in the analysis. The variables used for matching were age, gender, main medical history, ongoing medications, and intraoperative data. Of note, of the 27 PMI patients in Study I, 12 patients had to be excluded because of the missing blood samples. Previous randomized trials and systematic reviews have demonstrated that although perioperatively started beta blockers reduce myocardial ischemia and infarctions the risk for all-cause mortality increases mainly due to complications caused by bradycardia and hypotension (Devereaux *et al.*, 2008; Le Manach *et al.*, 2012; Mostafaife *et al.*, 2015; Blessberger *et al.*, 2018). However, in the majority of those studies, patients were treated with oral high-dose beta blockade that was started without titration of the dose. Data regarding individually adjusted beta blockade are very limited. Accordingly, Study IV was conducted. Esmolol was chosen because of the rapid onset of action, short half-life, and cardio-specificity, hypothesizing that the ability to rapidly adjust the dose and the cardio-specificity of the drug would provide the desirable effects without serious complications.

The literature search covered three major databases, PubMed, Ovid Medline, and the Cochrane Central Register for Controlled trials. The last search of the databases was performed on 2 May 2017. No restrictions were applied regarding the publication date or language. The search strategy is presented in Appendix 2. In addition to electronic search, the reference lists of relevant articles were hand-searched for potentially relevant studies. The study selection consisted of two phases: First, two authors (A.O. and L.V.) independently assessed the titles and abstracts of the identified reports. All reports considered as potentially pertinent by at least one of the assessors were retrieved as complete articles. Second, A.O. and L.V. independently assessed the retrieved complete articles and selected relevant ones for the final analysis. Discrepancies were resolved by discussion, and, if needed, the last author (E.W.) was consulted. The selection criteria are presented in Appendix 3. Database searches yielded a total of 249 reports, published

between 1973 and 2017, of which 56 full texts were reviewed. Ten additional potentially relevant studies were identified by searching the reference lists. After reviewing the total of 66 full texts, 52 reports were further excluded, 37 (56%) of which did not report the pre-defined outcome data. Of the remaining 14 studies, 11 reported only intraoperative outcomes and are summarized in Appendix 4. Finally, three reports presenting original data from three RCTs were included in the final analysis. The studies enrolled patients between 1997 and 2000 and were published in 1998 to 2000.

METHODS

Ethical considerations

The ethics committee of the Department of Surgery in Helsinki University Hospital provided ethics approval for all of the prospective observational studies (I-III) before starting the recruitment of patients. Studies I-III were conducted in Meilahti Hospital, Helsinki, Finland. The hospital is a tertiary care university hospital providing round-the-clock surgical care in the disciplines of abdominal, vascular, cardiac, and thoracic surgery. Written informed consent was obtained before study inclusion from all the patients or their next-of-kin in Studies I-III. Patients were informed that they could at any time withdraw their consent without explanation.

Evaluation of perioperative cardiac risk

In Studies I-III, every patient's perioperative cardiac risk was evaluated using the Gupta cardiac risk calculator (Gupta *et al.*, 2011). Development, validation, and the main principles of this model are explained in detail in the review of literature. The evaluation was done in retrospect, thus having no impact on monitoring or treatment decisions.

Perioperative monitoring and treatment protocols

In Study I, blood samples for high-sensitive cardiac troponin T (electrochemiluminescence immunoassay (ECLIA); Roche Diagnostics International Ltd., Rotkreuz, Switzerland) and an ECG were obtained five times perioperatively: before surgery, six hours after surgery, and on the first, second, and third postoperative mornings. Furthermore, together with TnT, 5 mL of EDTA plasma was taken for future analysis of EG markers and IL-6. In Study II, the same laboratory tests were conducted four times perioperatively: before surgery, and on the first, second, and third postoperative mornings. In both

studies, additional cardiac biomarkers and ECGs could be ordered at the treating physicians' discretions. In Study III, the blood samples and ECGs of Study I were used. Blood samples taken preoperatively and at six hours, and 24 hours postoperatively were analyzed for TnT, EG markers and IL-6. TnT levels were determined immediately after sampling from the vein or arterial line, while plasma for EG markers and IL-6 was centrifuged at 22°C at 3170 rpm for 10 min and stored at -80°C until analysis. Biomarkers of EG injury (sTM, syndecan-1, and VAP-1) and activation of the inflammatory system (IL-6) were analyzed at the Minerva Foundation Institute for Medical Research, Helsinki, Finland, by commercially available immunoassays according to the manufacturer's recommendations: sTM (Quantikine™ ELISA, R&D Systems Europe, Ltd., Abingdon, UK; the mean minimum detectable dose (MDD) 7.82 pg/mL, intra- and inter-assay coefficient of variation (CV) 2.3-3.6% and 5.7-8.0%); syndecan-1 (Human sCD138 (Syndecan-1) ELISA Kit, Nordic BioSite AB, Täby, Sweden; the mean MDD 4.94 ng/mL, intra- and inter-assay CV 6.2% and 10.2%); VAP-1 (Quantikine™ ELISA, R&D Systems Europe, Ltd., Abingdon, UK; the mean MDD 0.024 ng/mL, intra- and inter-assay CV 1.5-2.4% and 4.5-4.8%); IL-6 (Quantikine™ ELISA, R&D Systems Europe, Ltd. Abingdon, UK; the mean MDD < 0.70 pg/mL, intra- and inter-assay CV 1.6-4.2% and 3.3-6.4%).

In addition to daily ECG recordings, all patients in Study II were postoperatively monitored with a continuous ECG (Holter) recorder (SEER 12; Getemed, Teltow, Germany) to detect possible postoperative ischemia, and with a 3-axis accelerometer (Faros 360° eMotion; Mega Electronics Ltd., Kuopio, Finland) to enhance ischemia detection by distinguishing the ST-segment deviations caused by postural changes from the true ones. The monitoring was started immediately after arriving to the postanesthesia care unit (PACU) after surgery and continued for the next 72 hours or until discharge. The Holter monitoring stored data at one-minute intervals. Bipolar leads I, II, and III and unipolar leads aVL, aVR, aVF, and V1-V6 were used for Holter recording. The recordings were analyzed using an EK-Pro analysis program (GE Healthcare, Little Chalfont, UK), which stores data on patient's normal QRS-complexes and ST-segments (the calculated average during stable period) and marks abnormal ones relative to the baseline. The accelerometer continuously collected data on whether a patient was in an upright or supine position, lying on either side, or moving. The detection was based on the device's three sensitive axes that measure static (acceleration due to gravity) and dynamic (acceleration due to movement of the device) acceleration.

In Studies I and III, information about potential ischemic signs and symptoms was prospectively collected from electronic medical records, daily filled in by treating physicians and nurses. In Study II, patients were visited on the first to third postoperative mornings and asked about potential ischemic symptoms (chest pain, neck, jaw or arm discomfort, dyspnea, arrhythmias, or nausea) that were recorded.

The study group did not interfere with the perioperative treatment of the patients. However, a cardiologist (J.V.) formulated a local recommendation on PMI management based on national guidelines (Niemelä *et al.*, 2014) and the document was distributed to all physicians involved in the treatment of surgical patients.

Data sources

In Studies I-III, patients' demographic and medical baseline characteristics and current clinical data were obtained from electronic medical records (Uranus 8.4.3; CGI Group, Montreal, Quebec, Canada and Caresuite 8.2; Picis, Wakefield, MA, USA) to prospectively fill in an electronic case record form (eCRF) created for the study. Mortality dates were retrieved from the Finnish Population Register Centre and the causes of death were confirmed by reviewing the postoperative medical records.

In Study IV, the following data were extracted from the selected studies: 1.) the number of patients randomized to receive esmolol and their baseline demographic and clinical characteristics; 2.) the exclusion criteria of each study and information about dropouts and withdrawals; 3.) timing and duration of the intervention, bolus, or infusion type of administration, the dosage of the intervention drug, and potential unplanned co-interventions; 4.) the number of patients randomized into the no-esmolol group and their baseline demographic and clinical characteristics. To cover the existing literature and current options for treatment as comprehensively as possible, no restrictions regarding the potential treatment of the control group were applied. Instead, placebo, standard treatment, or treatment with oral beta blockers or with any other medication started for perioperative cardiac protection was considered as a comparator.

Outcome measures

In Study I, the primary outcomes were PMI and 90-day mortality. The secondary outcome was the performance of the Gupta cardiac risk calculator. In Study II, the primary outcomes were PMI and cumulative ischemic load (defined as an area under the function of magnitude of ischemic ST-segment deviation and ischemic time). The primary outcome of Study III was the magnitude of perioperative endothelial glycocalyx injury and its association with PMI. The primary outcomes of Study IV were 30-day major cardiac or renal complications, specifically myocardial infarction (MI), myocardial ischaemia, cardiac arrest, cardiac death, heart failure, unstable angina pectoris (UAP), new-onset arrhythmias, acute kidney injury (AKI), composite of renal events (AKI, need for renal replacement therapy (RRT), or worsening/development of chronic kidney failure), and composite of cardiac events (MI,

UAP, heart failure, new-onset arrhythmias, or cardiac death). The secondary outcomes were clinically significant bradycardia and/or hypotension (defined as a heart rate below 60 bpm or decreased heart rate together with clinical features suggestive of hypoperfusion and a blood pressure level requiring discontinuation of the study drug and/or administration fluid boluses or vasoactive medications), bronchospasm, stroke, neurologic sequelae, serious infection/sepsis, and all-cause mortality. Based on preliminary searches, a small number of eligible studies was expected, and thus, additional studies with only intraoperative follow-up, but reporting the predefined outcome measures were included. These studies were not included into the final meta-analysis. Appendix 4 presents the characteristics of the studies with only intraoperative follow-up data.

Definitions

In Studies I-III, the diagnosis of PMI was based on patients' baseline TnT level, repeated TnT measurements, ECGs, and ischemic signs or symptoms which were defined as the following: 1) ischemic symptoms (chest pain, arrhythmias, dyspnea), 2) cardiac imaging evidence of myocardial infarction, and 3) autopsy findings of acute or healing myocardial infarction. J.V. analyzed all of the ECGs of the patients with at least one TnT value above the upper reference limit (14 ng/L) and did the PMI diagnoses. The diagnoses were set according to the following criteria: 1) a rise and/or a fall of TnT with at least one value above 14 ng/L and 2) new ECG changes indicative to myocardial ischemia (significant ST-segment elevations in two contiguous leads, significant ST-segment depressions in two contiguous leads, T-inversions in two contiguous leads, and new left bundle branch block) and/or 3) other ischemic features.

In Study II, the analysis of ischemia was based on the magnitude of ST-segment deviation, measured at either 60 or 80ms after the J-point depending on the pulse rate. An ischemic event was defined as ST-segment depression or elevation ≥ 1mm persisting for over one minute and returning to the baseline for at least one minute, as suggested by Jernberg and colleagues (Jernberg et al., 2002). The data obtained from the accelerometer was manually combined with the Holter data, and the patient's position was considered in the ischemia diagnostics. J.V. analyzed all the Holter recordings including ischemic events and excluding artifacts and false-positive events. If ischemia occurred only in one lead, the patient's preoperative ECG was revised. If the preoperative ECG included comparative ST-segment deviations ≥ 1 mm, the postoperative deviation was not considered ischemia. If the preoperative ST-segment deviation was 0-1 mm in magnitude, this was subtracted from the postoperative deviation to obtain the accurate change.

Data completeness, risk of bias, and quality of evidence assessment

To assess the completeness of extracted data, a data completeness score based on 36 data items was calculated. The methodology of the scoring system and the data completeness scores of the included studies are presented in Appendix 5. In addition to the completeness of data, the quality of data was assessed using the GRADE approach (Guyatt *et al.*, 2008). GRADE includes the following domains: risk of bias, presence of reporting bias, inconsistency of data (heterogeneity), indirectness of data (was the outcome of interest tested in a population of interest for the intervention of interest), and imprecision of data (is the sample size smaller than optimal information size and/or is the CI wide, covering zones of no effect (RR 1.0), potential harm (RR 1.25), and potential benefit (RR 0.75). Based on these domains, GRADE classifies the level of confidence regarding an outcome as very low, low, moderate, or high. The risk of bias of the selected studies was assessed using the Cochrane tool (Higgins *et al.*, 2011) to ascertain the risk of bias of randomized trials. The following domains are taken into consideration in assessing the risk of bias: adequate random sequence generation, adequate allocation concealment, blinding of participants and personnel, blinding of outcome assessment, reporting of attritions or exclusions and re-inclusions, and selective outcome reporting. To further investigate the relevance of the results and the strength of evidence of the meta-analysis, trial sequential analysis (TSA) was conducted. TSA helps to apprehend if the detected effect holds, based on the cumulative evidence and to determine how many participants are needed to acquire the optimal information size.

Statistical analyses

The statistical analyses were performed using SPSS versions 22 and 23 (SPSS; Chicago, IL, USA) (I-III) and Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) (IV).

Categorical variables were compared with $\chi 2$ test or Fisher's exact test and continuous variables with Mann-Whitney U-test (I-II, III) or Student's t-test (II), as appropriate. Data are presented as absolute numbers (percentage with 95% confidence intervals [CIs]), as means (standard deviation [SD]), or as medians (interquartile ranges [IQRs]). The survival of patients with and without PMI was investigated with Kaplan-Meier analysis, and the survivals were compared using Mantel-Cox log rank test (I). The predictive abilities of the Gupta cardiac risk calculator (I), ischemic load (II), and endothelial glycocalyx markers and interleukin-6 were tested by calculating areas under receiver operating characteristic curves (AUCs) with 95% CIs. The best cut-off points were identified with the Youden method, and these cut-off points were used to calculate sensitivity, specificity, positive (LR+) and

negative (LR-) likelihood ratios. To compare perioperative glycocalyx injury in patients with and without PMI (III), four propensity-matched controls for each PMI patient were selected. A propensity score was calculated for each patient based on demographic and medical data. Variables included in the propensity matching are presented in the results section. Briefly, these variables includ age, gender, main medical history, medications, and intraoperative data.

To assess the magnitude of differences between PMI and non-PMI patients' preoperative and 6- and 24-hour postoperative values and the highest values of EG markers and IL-6, Hodges-Lehman estimators with 95% CIs were calculated (III). In the meta-analysis (IV) an individual patient was used as the unit of analysis and the analysis was based on intention-to-treat data from the individual studies.

Risk ratios (RRs) were calculated as summary measures. Heterogeneity among studies was assessed with Cochrane Q test ($\chi 2$). Inconsistency across the individual studies was determined by calculating I2 statistics, which was interpreted according to the following guidelines: 0-40% may not be important, 30-60% may present moderate heterogeneity, 50-90% represents substantial heterogeneity, and 75-100% represents considerable heterogeneity (Higgins *et al.*, 2013). Fixed effect or random effects modelling was used for analysis, as appropriate. The random effects model was applied if considerable heterogeneity among studies was identified. The results are reported in forest plots with 95% CIs. A two-sided p-value of < 0.05 was considered statistically significant (I-IV).

RESULTS

PERIOPERATIVE MYOCARDIAL INFARCTION IN NON-CARDIAC SURGERY PATIENTS – AN ANALYSIS FROM A FINNISH TERTIARY CARE HOSPITAL

At the time of enrollment, 570 eligible patients underwent a non-cardiac surgery. Altogether 385 patients (67.5% of the all the eligible) consented to participate in the study and formed the cohort with systematic ischemia screening. Of these patients, 172 underwent vascular, 80 thoracic, and 133 gastrointestinal surgery. Ten patients (1.8% of the all the eligible) declined to participate and were excluded from the study. The 175 patients who could not consent or whose consent could not be ascertained formed the cohort with routine perioperative care.

Cohort with systematic ischemia screening

A perioperative TnT release > 14 ng/l was observed in 75 patients (19.5%) and 27 patients (7%) sustained PMI, all of which of the ST-segment depression-type. The incidence of PMI was highest in vascular surgery patients: 19 of 172 (11%) versus 8 of 133 (6%) and 0 of 80 (0%) in gastrointestinal and thoracic surgery patients, respectively ($p<0.01$).

Table 4 presents the clinical characteristics of the patients with and without PMI. Patients who sustained PMI had more pre-existing cardiovascular morbidity, higher ASA class, lower nadir hemoglobin (Hb) during hospitalization, and larger intraoperative vasopressor load.

Table 4. *Characteristics of the ischemia surveillance patients with and without PMI.*

		All patients N=385 n (%) or median [IQR	**PMI** N=27 n (%) or median [IQR]	**No PMI** N=358 n (%) or median [IQR	***p*-value**
Age (years)		69 [64-78]	71 [65-79]	69 [63-77]	NS
Gender (male)		215 (55.8)	16 (59.3)	200 (55.9)	NS
Comorbidity	CAD	85 (22.1)	12 (44.4)	73 (20.4)	0.007
	Heart failure	44 (11.4)	5 (18.5)	39 (10.9)	NS
	PVD	102 (26.5)	15 (55.6)	87 (24.3)	0.001
	Hypertension	232 (60.3)	17 (63.0)	215 (60.1)	NS
	COPD	48 (12.5)	7 (25.9)	41 (11.5)	NS
	DM	107 (27.8)	7 (25.9)	100 (27.9)	NS
	Current malignancy	77 (20.0)	0	77 (21.5)	0.004
Prior	Acute MI	44 (11.4)	7 (25.9)	37 (10.3)	0.05
	Coronary revascularisation	51 (13.2)	6 (22.2)	45 (12.6)	NS
	Stroke	85 (15.2)	6 (22.2)	79 (22.1)	NS
ASA classification	II	43 (11.2)	0	43 (12.0)	NS
	III	219 (56.9)	11 (40.7)	208 (58.1)	NS
	IV-V	118 (30.6)	16 (59.3)	102 (28.5)	0.002
Preoperative medication	Statin	199 (51.7)	12 (44.4)	187 (52.2)	NS
	β-blocker	180 (46.8)	17 (63.0)	163 (45.5)	NS
	ACEI/A2RB	198 (51.4)	15 (55.6)	183 (51.1)	NS
	Acetylsalicylic acid	176 (45.7)	13 (48.1)	163 (45.5)	NS
	Clopidogrel	31 (8.1)	3 (11.1)	28 (7.8)	NS
Gupta score*		0.79 [0.49-2.05]	2.6 [0.84-3.91]	0.78 [0.48-1.83]	<0.0001
Urgent/ Emergency operation		221 (57.4)	20 (74.1)	201 (56.1)	NS
Preoperative laboratory values	Hb (g L^{-1})	131 [115-143]	126 [108-145]	131 [115-143]	NS
	Thrombocytes (x 10^9)	238 [193-304]	223 [174-287]	237 [193-300]	NS
	Creatinine (µmol L^{-1})	74 [62-93]	84 [64-125]	75 [62-93]	NS
	TT (%)	92 [73-109]	86 [58-112]	93 [74-109]	NS
	TnT (ng L^{-1})	13 [8-23]	40 [15-80]	12 [8-21]	<0.0001
Vasopressor load during the day of surgery (mg)		0.48 [0-1.56]	1.34 [0.48-6.76]	0.43 [0-1.42]	<0.0001
Nadir Hb during hospitalization (g L^{-1})		105 [89-120]	92 [77-104]	105 [90-120]	0.005

* Gupta PK, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation. 2011;124:381-7.

Abbreviations: PMI, perioperative myocardial infarction; IQR, interquartile range; CAD, coronary artery disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; MI, myocardial infarction; ASA, American Society of Anesthesiologists; ACEI, angiotensin-converting enzyme inhibitor; A2RB, angiotensin II receptor blocker; Hb, haemoglobin concentration; TT, thromboplastin time; TnT, troponin T.

Notably, 182 (47.3%) of the patients had a preoperatively elevated TnT. Preoperative TnT values were significantly higher in the patients who sustained PMI ($p< 0.01$). The majority of PMIs (16 of 27, 59.3%) occurred on the first or second postoperative day. Only six (22.2%) patients who sustained PMI had symptoms of myocardial ischemia. Four patients underwent a coronary angiography after the diagnosis of PMI and for three of them a coronary revascularization was performed. Cardiovascular medication was optimized in four patients. In the remaining 19 patients, the diagnosis of PMI did not lead to any interventions.

The 90-day mortality was 7.3% among all the patients. The mortality rate was significantly higher in patients who sustained PMI than in those who did not, 29.6% versus 5.6%, ($p< 0.01$). Of the deaths in PMI patients, 87.5% occurred during the first 23 postoperative days, while the deaths of non-PMI patients were distributed evenly over the entire 90-day period. Six (75%) of the eight deaths in PMI patients had a vascular cause. The 90-day mortality of the patients with a perioperative troponin release, but without other ischemic signs or symptoms was 10.4%.

The Gupta cardiac risk calculator predicted PMI with an AUC of 0.73 (95% CI: 0.64-0.81). The best cut-off value was 2.55 with sensitivity, specificity, LR+, and LR- of 0.57, 0.81, 3.01 (95% CI: 2.02-4.49), and 0.55 (95% CI: 0.36-0.84), respectively. In addition, the performance of the cardiac risk index in predicting 90-day mortality was tested. The index predicted 90-day mortality with an AUC of 0.75 (95% CI: 0.66-0.85). The best cut-off value was 1.85 with sensitivity, specificity, LR+, and LR- of 0.71, 0.76, 3.0 (95% CI: 2.23-4.04), and 0.38 (95% CI: 0.21-0.68), respectively.

Cohort with routine perioperative care

The patients whose consent was missing did not differ from the cohort with systematic ischemia screening in terms of baseline characteristics. However, they were more often operated on outside of office hours and had more urgent/emergency surgeries. The distribution of the types of surgeries was similar in both cohorts.

TnT measurements were ordered at treating physicians' discretion in 39 (22.3%) of the 175 patients. Three patients (1.7%) sustained PMI. The 90-day mortality was 13.1%.

SILENT POSTOPERATIVE ISCHEMIA IN PATIENTS WITH HIGH PERIOPERATIVE CARDIAC RISK

Ninety patients meeting inclusion criteria underwent a vascular surgery during enrollment. Thirty-three patients (36.7%) were not enrolled in the study for the following reasons: 2 did not consent, 12 had pre-existing conduction defects precluding the ST-segment analysis, and 19 could not be enrolled due to logistic reasons. As the continuous ECG (cECG) recordings were reviewed, six additional patients had to be excluded because of unreadable cECGs. Thus, the final cohort included 51 patients. The clinical characteristics of the patients are presented in Table 5.

Table 5. *Characteristics of the patients (n=51) with and without postoperative ischemia.*

		All patients N=51 n (%) or median [IQR]	**Ischemia** N=17 n (%) or median [IQR]	**No ischemia** N=34 n (%) or median [IQR]	***p*-value**
Age		74 [69-77]	76 [72-79]	73 [69-77]	NS
Gender (male)		29 (56.9)	8 (47.1)	21 (61.8)	NS
Comorbidity	CAD	24 (47.1)	8 (47.1)	16 (47.1)	NS
	Heart failure	7 (13.7)	2 (11.8)	5 (14.7)	NS
	Kidney failure	7 (13.7)	1 (5.9)	6 (17.6)	NS
	PVD	45 (88.2)	16 (94.1)	29 (85.3)	NS
	Hypertension	46 (90.2)	15 (88.2)	31 (91.2)	NS
	DM	18 (35.3)	6 (35.3)	12 (35.3)	NS
	COPD	7 (13.7)	1 (5.9)	6 (17.6)	NS
	Current malignancy	6 (11.8)	2 (11.8)	4 (11.8)	NS
Prior	Acute MI	16 (31.4)	6 (35.3)	10 (29.4)	NS
	Coronary revascularisation	14 (27.5)	6 (35.3)	8 (23.5)	NS
	Stroke/TIA	12 (23.5)	5 (29.4)	7 (20.6)	NS
ASA classification	II	1 (2.0)	0	1 (2.9)	NS
	III	25 (49.0)	11 (64.7)	14 (41.2)	NS
	IV-V	25 (49.0)	6 (35.3)	19 (55.9)	NS
Preoperative medication	β-blocker	40 (78.4)	12 (70.6)	28 (82.4)	NS
	Statin	44 (86.3)	14 (82.4)	30 (88.2)	NS
	Nitrates	7 (13.7)	3 (17.6)	4 (11.8)	NS
	ACEI/AR2B	37 (72.5)	12 (70.6)	25 (73.5)	NS
	CCB	22 (43.1)	6 (35.3)	16 (47.1)	NS
	Acetylsalicylic acid	42 (82.4)	17 (100)	25 (73.5)	0.05
	Clopidogrel	13 (25.5)	5 (29.4)	8 (23.5)	NS

Table 5. *Characteristics of the patients (n=51) with and without postoperative ischemia.*

Gupta score*		1.76 [0.79-3.60]	1.63 [0.75-2.98]	1.93 [0.82-3.62]	NS
Urgent/Emergency operation		14 (27.5)	4 (23.5)	10 (29.4)	NS
Preoperative laboratory values	Hb (g L^{-1}) Thrombocytes (x 10^9) Creatinine (µmol L^{-1}) TT (%)	126 [111-131] 264 [182-349] 81 [66-97] 96 [83-109]	117 [106-130] 300 [210-400] 82 [63-100] 96 [87-111]	126 [114-132] 243 [177-328] 81 [67-95] 96 [81-110]	NS NS NS NS
Vasopressor load during the day of surgery (mg)		1.42 [0.66-2.43]	1.42 [0.30-1.88]	1.50 [0.69-2.65]	NS
Nadir Hb during hospitalization (g L^{-1})		89 [81-105]	87 [80-95	93 [83-114]	0.06

* Gupta PK, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation. 2011;124:381-7.

Abbreviations: IQR, interquartile range; CAD, coronary artery disease; PVD, peripheral vascular disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIA, transient ischemic attack; ASA, American Society of Anesthesiologists; ACEI, angiotensin-converting enzyme inhibitor; A2RB, angiotensin II receptor blocker; CCB, calcium channel blocker; Hb, hemoglobin concentration; TT, thromboplastin time.

Continuous ECG monitoring

The total time of monitoring was 64.0±20.2 hours per patient. Seventeen patients (33.3%) had ischemic episodes, 11.9±32.9 episodes per patient, range 0 to 184, all of which were of ST-segment depression type. The details of postoperative ischemia in patients with and without PMI are summarized in Table 6.

Table 6.
Details of postoperative myocardial ischemia in patients with and without PMI.

	All patients N=51 mean (SD	**PMI** N=5 mean (SD)	**No PMI** N=46 mean (SD)	***p*-value**
Longest ischemia duration (min)	7.2 (20.4)	22.6 (27.4)	5.6 (19.1)	0.001
Cumulative ischemia duration (min)	42.9 (127.0)	224.0 (311.1)	23.3 (72.7)	0.001
Ischemia load (μV*minute)	913.2 (2797.3)	4475.6 (6241.8)	526.0 (1915.1)	0.001
Preoperative TnT (ng L^{-1})	32.7 (70.1)	112.2 (200.9)	24.0 (33.1)	0.002
Highest TnT (ng L^{-1})	54.9 (107.5)	244.2 (278.7)	34.4 (38.9)	0.16

Abbreviations: PMI, perioperative myocardial infarction; SD, standard deviation; TnT, troponin T.

Most of the ischemic episodes occurred during the second postoperative day. Only 17.6% of the postoperative ischemia associated with ischemic symptoms. The mean heart rate during non-ischemic stages of monitoring was higher in patients with postoperative ischemia than in patients without postoperative ischemia (90.9±17.6 beats per minute (bpm) versus 71.7±12.1 bpm, $p<0.001$). Ischemic episodes were preceded by an increase in heart rate (Δ heart rate = 3.8±5.7 bpm, range -1.6 to 16). No significant differences emerged in the pre-ischemic changes of the heart rate in patients with and without PMI.

PMI

Five patients (9.8%) sustained PMI. All the PMIs were diagnosed during the first three postoperative days. Three patients had symptoms of angina pectoris. The cumulative ischemia duration, the duration of the longest ischemic event, IL, and preoperative TnT values were higher in patients

who sustained PMI than in those who did not (Table 6). IL predicted PMI with an AUC of 0.87 (95% CI: 0.75-0.99). The best cut-off value was 12.5 µVxmin with sensitivity, specificity, LR+ and LR- of 1.0, 0.74, 3.83 (95% CI: 2.36-6.23), and 0.0, respectively.

Table 7 summarizes the performance of cECG-derived measurements in predicting PMI.

Table 7. *The performance of cECG-derived parameters in predicting PMI.*

	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	LR+ (95%CI)	LR- (95% CI)	**PPV%**	**NPV%**
Ischemic load	0.87 (0.75-0.99)	12.5 µVxmin	1.00	0.74	3.83 (2.36-6.23)	0	29.4	100
Ischemic time	0.88 (0.76-0.99)	1.25 min	1.00	0.74	3.83 (2.36-6.23)	0	29.4	100
Longest ischemic event	0.87 (0.76-0.98)	1.34 min	1.00	0.76	4.18 (2.50-7.01)	0	31.3	100
HR at onset of ischemia	0.78 (0.55-1.00)	89.3 bpm	0.8	0.83	4.60 (2.13-9.90)	0.24 (0.04-1.40)	33.3	97.4

Sensitivity, specificity, positive and negative predictive values were calculated using optimal cut-off values determined with Youden index.

Abbreviations: cECG, continuous electrocardiographic monitoring; PMI, perioperative myocardial infarction; AUC, area under receiver operating characteristics curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; HR, heart rate.

Lead sensitivity

The sensitivities of the cECG leads and their combinations in detecting postoperative ischemia are shown in Table 8.

Table 8.
Sensitivity of ECG leads and lead combinations in detecting postoperative ischemia during continuous monitoring.

Lead	In the beginning of ischemia (%)		p-value
V4	51.4		
II	39.4	II vs. V4	0.096
aVF	33.8	aVF vs. V4	< 0.001
V5	24.7	V5 vs. V4	< 0.001
	At peak ischemia (%)		
V4	45.7		
II	25.2	II vs. V4	< 0.001
V5	17.4	V5 vs. V4	< 0.001
Abbreviations: ECG, electrocardiogram			

Lead V4 outperformed V5 in ischemia detection sensitivity. At the beginning of ischemia, the best detection sensitivity (97.2%) was acquired by combining the leads V4, V5, II, and aVF.

Movement analysis

The data recorded by the accelerometer were used to classify the following seven postures: supine, prone, on the right and left side, standing/sitting, half-sitting, and moving. The correlation between posture and simultaneous ST-segment deviation was analyzed in individual patients and in the whole cohort. Additionally, the ischemic alarms to which a change in the posture could be associated were studied. There was not a clear correlation between postures and ST-segment deviation either in individual patients or in the whole cohort. However, patients did not cycle through all the postures, and thus, the postural variable was distributed unequally. Six ischemic alarms associated with a turn from back to side were observed. Combining the cECG and accelerometer data suggested that all of the alarms were true positives, no movement artifacts were found.

ASSOCIATION OF ENDOTHELIAL INJURY AND SYSTEMIC INFLAMMATION WITH PERIOPERATIVE MYOCARDIAL INFARCTION

Seventy-five patients (15 who sustained PMI and 60 matched controls) were included in the study. To assess the generalizability of the results, the baseline characteristics of the primary study patients with all plasma samples taken were compared with the baseline characteristics of those with lacking plasma samples. Except for differences in the number of urgent/emergency surgeries, vasopressor support, ASA class, and perioperative cardiac risk, patients were comparable in terms of baseline characteristics (Appendix 6).

PMI

The 90-day mortality of PMI patients was 20%, compared with 8.3% in non-PMI patients. The median values of EG markers and IL-6 are presented in Table 9.

Table 9.
The median values of EG markers and IL-6 measured in PMI patients and propensity-matched controls.

	PMI N=15 median [IQR]	**No PMI** N=60 median [IQR]	***p*-value**	**HL** (95% CI)
Preoperative				
sTM	3.95 [3.13-7.02]	4.17 [3.47-4.74]	0.87	-60 (-1014.0, 751.0)
Syndecan-1	0.06 [0.05-0.09]	0.06 [0.04-0.08]	0.17	-9.0 (-23.0, 5.5)
VAP-1	0.36 [0.30-0.51]	0.36 [0.30-0.47]	0.66	-13.5 (-86.0, 56.0)
IL-6	0.03 [0.01-0.09]	0.007 [0.003-0.03]	0.008	-13.3 (-27.3, -3.6)
6h postoperative				
sTM	3.50 [2.94-5.25]	4.00 [3.39-4.69]	0.47	200.0 (-501.0, 846.0)
Syndecan-1	0.10 [0.06-0.12]	0.07 [0.04-0.12]	0.15	-13.4 (-38.3, 7.1)
VAP-1	0.32 [0.25-0.38]	0.33 [0.26-0.42]	0.57	18.0 (-46.0, 78.0)
IL-6	0.21 [0.05-0.29]	0.07 [0.03-0.12]	0.013	-72.1 (-182.3, -12.2)
24h postoperative				
sTM	4.05 [3.71-5.32]	4.30 [3.65-5.07]	0.94	44.5 (-661.0, 645.0)
Syndecan-1	0.07 [0.05-0.1]	0.07 [0.05-0.09]	0.44	-7.0 (-24.4, 11.2)
VAP-1	0.30 [0.26-0.40]	0.33 [0.26-0.42]	0.53	16.5 (-35.0, 74.0)
IL-6	0.21 [0.10-0.32]	0.07 [0.02-0.15]	0.006	-93.2 (-199.2, -23.1)
Highest				
sTM	4.19 [3.72-7.02]	4.37 [3.65-5.34]	0.87	-76.5 (-920.0, 646.0)
Syndecan-1	0.11 [0.06-0.14]	0.07 [0.06-0.11]	0.12	-19.1 (-48.9, 4.8)
VAP-1	0.38 [0.30-0.51]	0.37 [0.30-0.47]	0.67	-15.5 (-90.0, 57)
IL-6	0.24 [0.10-0.35]	0.10 [0.04-0.19]	0.022	-93.1 (-213.0, -12.0)

Abbreviations: EG, endothelial glycocalyx; IL-6, interleukin-6 (pg L^{-1}); PMI, perioperative myocardial infarction; HL, Hodges-Lehman estimator; IQR, interquartile range; CI, confidence interval; sTM, soluble thrombomodulin (pg L^{-1}); Syndecan-1 (ng L^{-1}); VAP-1, vascular adhesion protein 1 (ng L^{-1}).

The patients with PMI had higher IL-6 levels during the whole 24-hour follow-up. However, sTM, syndecan-1, and VAP-1 levels were comparable in patients with and without PMI at all time points.

Association of systemic inflammation and EG injury with perioperative TnT release

Figure 5 illustrates the kinetics of EG markers and IL-6 in patients with and without PMI.

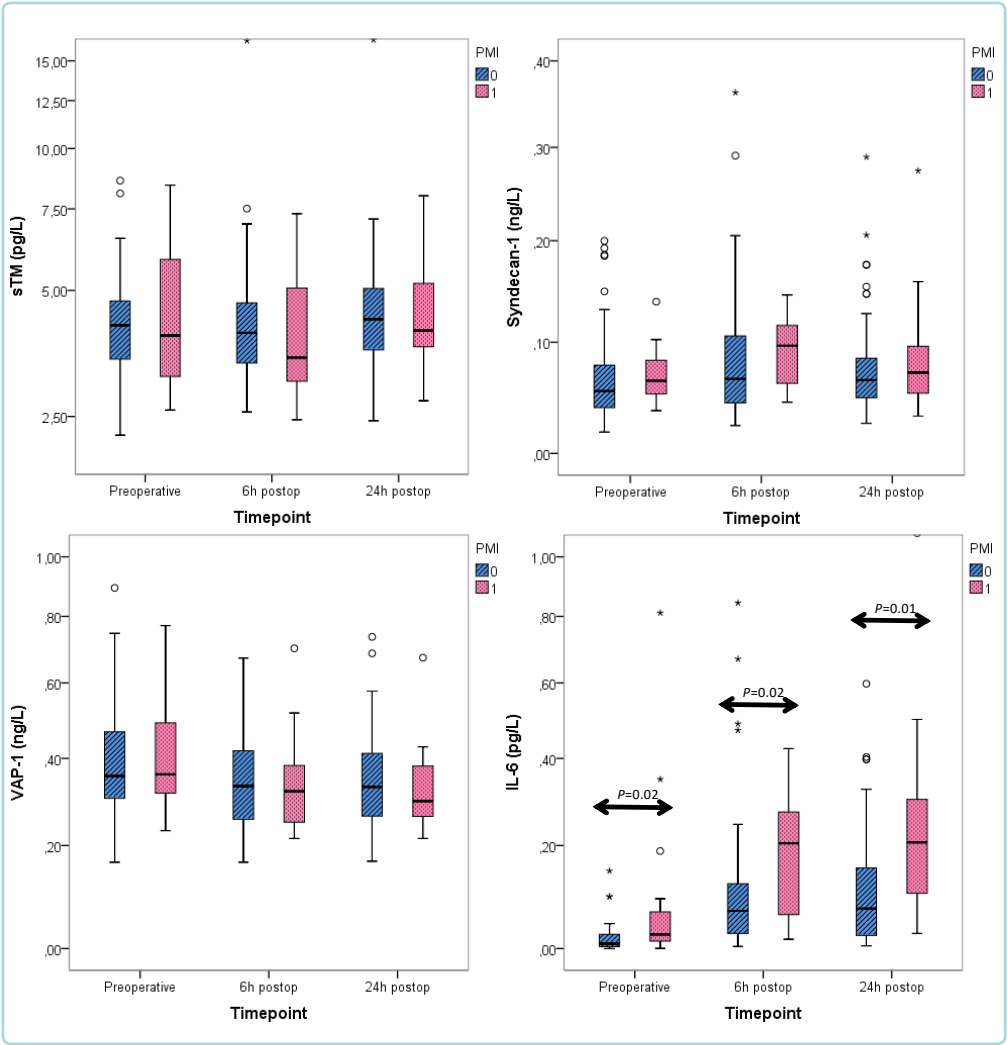

Figure 5. *The kinetics of endothelial glycocalyx markers and interleukin-6 in patients with and without PMI. Non-transformed values are presented on a logarithmic scale. Bars represent medians with interquartile ranges. T-bars represent values 1.5 times greater than the interquartile range. PMI, perioperative myocardial infarction; sTM, soluble thrombomodulin; VAP-1, vascular adhesion protein 1; IL-6, interleukin-6.*

IL-6 levels of PMI patients were significantly higher across all the time points (p=0.002, p=0.002, and p=0.001, respectively). There were no differences in sTM, syndecan-1, or VAP-1 concentrations between PMI and non-PMI patients. The potential correlations between TnT, IL-6, and EG markers in patients with and without PMI were tested with Spearman's rho.

The correlations are presented in Tables 10A and 10B.

Table 10A.
Correlations of EG markers and IL-6 with preoperative, 6h and 24h post-operative TnT values by Spearman's rho in patients with PMI (N=15).

	PMI N=15 median [IQR]	**No PMI** N=60 median [IQR]	***p*-value**	**HL** (95% CI)
sTM	Correlation Coefficient	0.48	**0.51**	0.46
	Sig. (2-tailed)	0.07	**0.05**	0.09
IL-6	Correlation Coefficient	**0.53**	**0.64**	**0.51**
	Sig. (2-tailed)	**0.04**	**0.01**	**0.05**
Syndecan-1	Correlation Coefficient	0.49	0.32	0.47
	Sig. (2-tailed)	0.06	0.25	0.07
VAP-1	Correlation Coefficient	-0,15	-0.31	-0.10
	Sig. (2-tailed)	0.59	0.27	0.72
sTM_6h	Correlation Coefficient	0.44	0.49	0.41
	Sig. (2-tailed)	0.10	0.07	0.12
IL-6_6h	Correlation Coefficient	0.44	0.49	0.41
	Sig. (2-tailed)	0.10	0.07	0.12
Syndecan-1_6h	Correlation Coefficient	0.44	0.49	0.41
	Sig. (2-tailed)	0.10	0.07	0.12
VAP-1_6h	Correlation Coefficient	0.44	0.49	0.41
	Sig. (2-tailed)	0.10	0.07	0.12
sTM_24h	Correlation Coefficient	**0.44**	**0.49**	**0.41**
	Sig. (2-tailed)	**0.10**	**0.07**	**0.12**
IL-6_24h	Correlation Coefficient	0.44	0.49	0.41
	Sig. (2-tailed)	0.10	0.07	0.12
Syndecan-1_24h	Correlation Coefficient	0.44	0.49	0.41
	Sig. (2-tailed)	0.10	0.07	0.12
VAP-1_24h	Correlation Coefficient	0.44	0.49	0.41
	Sig. (2-tailed)	0.10	0.07	0.12

Abbreviations: EG, endothelial glycocalyx; IL-6, interleukin-6; TnT, troponin T; PMI, perioperative myocardial infarction; sTM, soluble thrombomodulin; VAP-1, vascular adhesion protein 1.

Table 10B.
Correlations of EG markers and IL-6 with preoperative, 6h and 24h postoperative TnT values by Spearman's rho in patients without PMI (N=60).

		TnT	TnT_6h	TnT_24h
sTM	Correlation Coefficient	**0.54**	**0.48**	**0.52**
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**
IL-6	Correlation Coefficient	**0.35**	**0.26**	0.21
	Sig. (2-tailed)	**0.006**	**0.05**	0.1
Syndecan-1	Correlation Coefficient	0.15	0.1	0.1
	Sig. (2-tailed)	0.25	0.47	0.43
VAP-1	Correlation Coefficient	-0.03	0.01	0.1
	Sig. (2-tailed)	0.79	0.97	0.5
sTM_6h	Correlation Coefficient	**0.48**	**0.43**	**0.46**
	Sig. (2-tailed)	**<0.001**	**0.001**	**<0.001**
IL-6_6h	Correlation Coefficient	0.14	0.32	0.23
	Sig. (2-tailed)	0.29	0.01	0.08
Syndecan-1_6h	Correlation Coefficient	-0.01	0.01	-0.02
	Sig. (2-tailed)	0.95	0.96	0.89
VAP-1_6h	Correlation Coefficient	-0.17	-0.15	-0.07
	Sig. (2-tailed)	0.21	0.27	0.62
sTM_24h	Correlation Coefficient	**0.51**	**0.44**	**0.49**
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**
IL-6_24h	Correlation Coefficient	**0.36**	**0.37**	**0.34**
	Sig. (2-tailed)	**0.005**	**0.003**	**0.007**
Syndecan-1_24h	Correlation Coefficient	-0.11	-0.13	-0.16
	Sig. (2-tailed)	0.4	0.33	0.23
VAP-1_24h	Correlation Coefficient	-0.16	-0.12	-0.05
		0.23	0.35	0.72

Abbreviations: EG, endothelial glycocalyx; IL-6, interleukin-6; TnT, troponin T; PMI, perioperative myocardial infarction; sTM, soluble thrombomodulin; VAP-1, vascular adhesion protein 1.

Preoperative IL-6 correlated positively with preoperative, 6h postoperative, and 24h postoperative TnT in PMI patients (p=0.05). Furthermore, 24-hour postoperative sTM correlated positively with preoperative and 6-hour, and 24-hour postoperative TnT (p=0.05) in PMI patients. In patients without PMI, sTM and TnT levels correlated positively preoperatively (p<0.001), 6h postoperatively (p=0.001) and 24h postoperatively (p<0.001).

The association of systemic inflammation and EG injury with PMI

The association of systemic inflammation and EG injury with PMI
The highest values of each marker were used in the analysis. None of the EG markers were predictive for PMI. IL-6 predicted PMI with an AUC (95% CI) of 0.69 (0.54-0.85) (p=0.02). The best cut-off value for IL-6 was 0.24 pg/L with sensitivity, specificity, LR+ and LR- of (95% CI) of 0.53, 0.85, 3.56 (1.65-7.65), and 0.55 (0.32-0.95), respectively.

Study characteristics

The characteristics of the three included studies are summarized in Table 11.

Table 11.
Characteristics of the studies included in the meta-analysis.

	Raby	Urban	Balser
Journal	Anesth Analg	Anesth Analg	Anesthesiology
Year of publication	1999	2000	1998
Study design	Double-blind	Open	Open
No. of patients (esmolol)	15	52	34
No. of patients (control)	11	55	30*
No. of groups	2	2	2
Preoperative beta blocker administration, % of randomised patients (esmolol/control)	33/36	27/29	39/30
Intervention	Esmolol 100–300 µg/kg/min	Esmolol 250 mg/h	Esmolol with a bolus of 12.5–250 mg followed by an infusion of 50–150 µg/kg/min
Length of administration	48 hours	18-24 hours[δ]	12 hours
Starting time of intervention	After surgery	After surgery	After surgery
Control	Placebo	Placebo	Diltiazem with a bolus of 20–45 mg followed by an infusion of 10–15 mg/h
Haemodynamic target	Postoperative HR 20% below the ischaemic threshold (minimum of 60 bpm)	Postoperative HR below 80 bpm	Postoperative HR between 80–100 bpm
No. of patients treated with any beta-blockers in the control group	9 (81.8)	18 (32.7)	0
Type of surgery	Peripheral vascular	Orthopaedic	Non-cardiac[¶]
Urgency	NR	Elective	NR

Table 11.
Characteristics of the studies included in the meta-analysis.

Outcomes n (%)	Esmolol	Control	Esmolol	Control	Esmolol	Control
MI	0	1 (9.1)	1 (1.9)	3 (5.5)	NR	NR
Myocardial ischaemia	5 (33.3)	8 (72.7)	3 (5.8)	8 (14.5)	NR	NR
Cardiac arrest	NR	NR	NR	NR	NR	NR
Cardiac death	0	0	NR	NR	NR	NR
Heart failure	0	0	NR	NR	NR	NR
UAP	1 (6.6)	0	NR	NR	NR	NR
New-onset arrhythmias	NR	NR	NR	NR	NR	NR
Composite of cardiac events (1)	1 (6.7)	1	7 (13.5)	12 (21.8)	NR	NR
AKI	NR	NR	NR	NR	NR	NR
Composite of renal events (2)	NR	NR	NR	NR	NR	NR
Bradycardia	NR	NR	3 (5.8)	0	0	0
Hypotension	NR	NR	1 (1.9)	0	2 (5.9)	1 (3.3)
Stroke	NR	NR	NR	NR	NR	NR
Bronchospasm	NR	NR	NR	NR	NR	NR
Comatose symptoms	NR	NR	NR	NR	NR	NR
Serious infection/ sepsis	NR	NR	NR	NR	NR	NR

* One patient included at two separate times.

[δ] On the first postoperative morning esmolol was switched to oral metoprolol (starting dose 25 mg twice a day) that was titrated to keep HR below 80 bpm and continued for the next 48 hours.

[¶] Surgeries including major abdominal, urologic, thoracic, vascular, neurosurgery, and general surgery operations.

Abbreviations: HR, heart rate; bpm, beats per minute; NR, not reported; MI, myocardial infarction; UAP, unstable angina pectoris; AKI, acute kidney injury. (1) MI, unstable angina, heart failure, new-onset arrhythmias, cardiac death (2) AKI, need for renal replacement therapy, worsening development of chronic kidney failure.

The studies included a total of 196 patients, of whom 101 received esmolol and 96 received control drug or placebo. Placebo was given to 66 of 96 controls (68.8%); the remaining 30 patients received diltiazem. In a study by Balser and colleagues, one patient was included at two separate times and at both times was randomized to receive the control drug; consequently, from this

study 64 patients were taken into analysis. However, outcome measures were analyzed and reported using 63 individual patients. All studies investigated a cohort from a single center and had an inadequate sample size to reach statistically significant results in clinically relevant outcome measures.

Data synthesis and risk of bias

The results of meta-analysis are graphically presented in Figures 6A and 6B and summarized in Table 12. Figures 6A and 6B also present the assessed risk of bias of the studies.

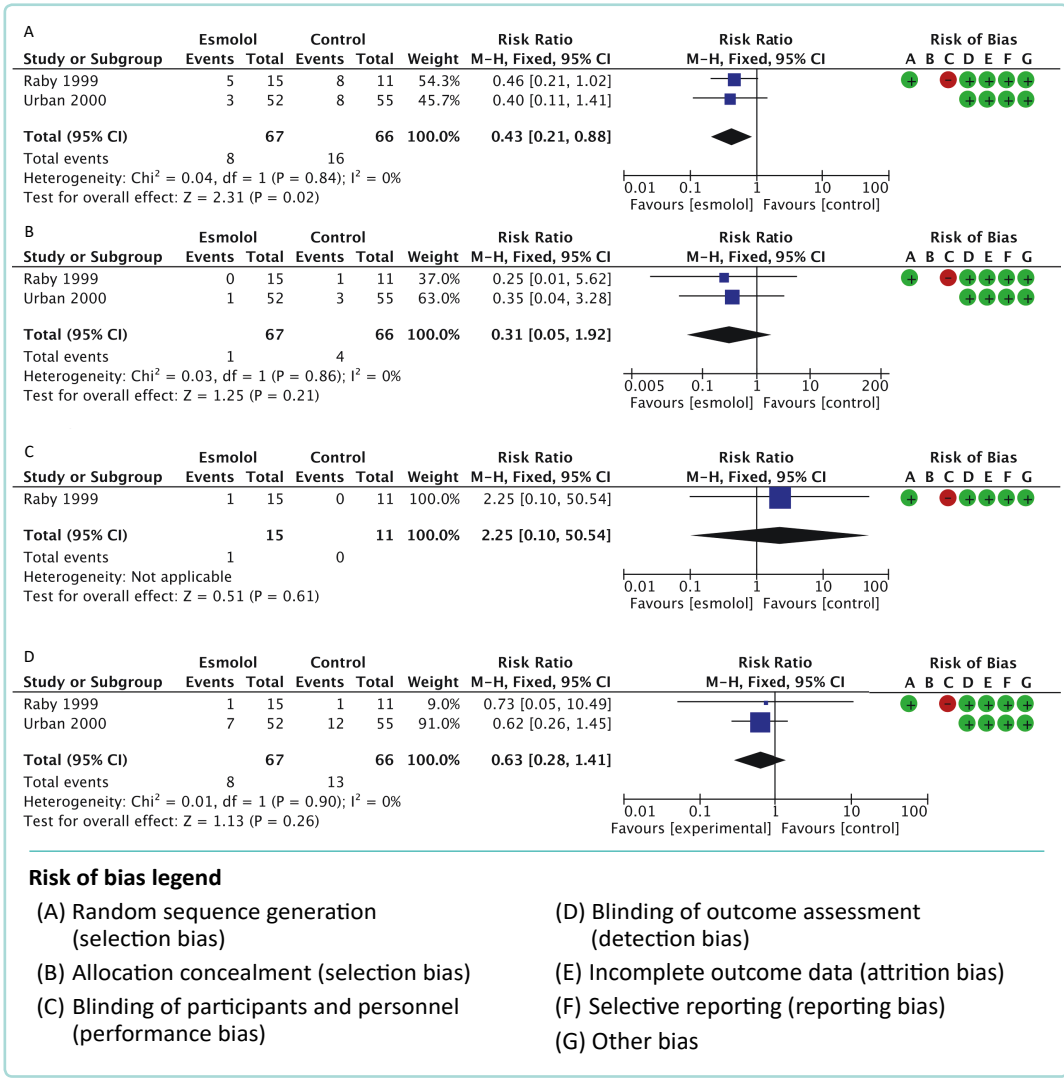

Figure 6A. *Forest plots of the comparisons: (panel A) myocardial ischemia, (panel B) myocardial infarction, (panel C) unstable angina pectoris, (panel D), a composite of cardiac events.*

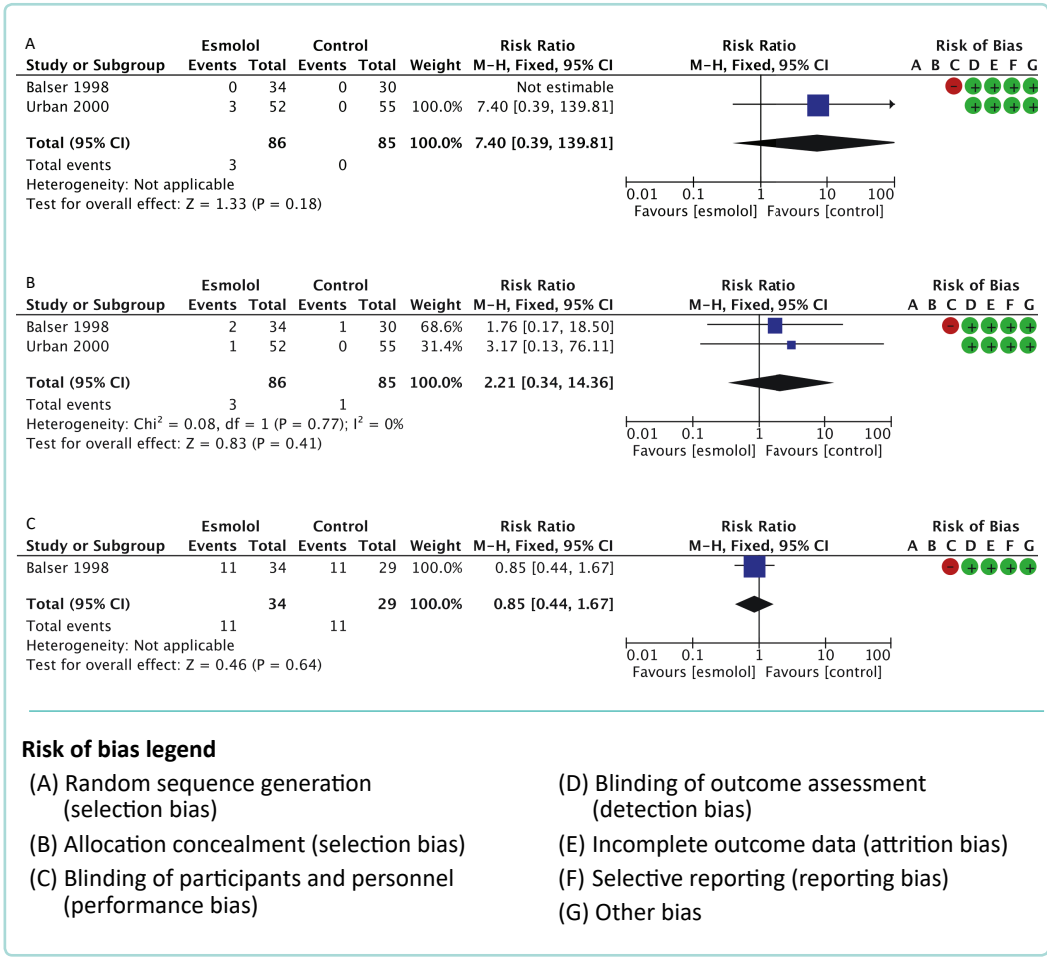

Figure 6B. *Forest plots of the comparisons: (panel A) bradycardia, (panel B) hypotension, (panel C) all-cause mortality.*

Table 12.
Summary of the main results.

	Number of trials	**Esmolol** n/N (%)	**Control** n/N (%)	**NNT/NNH** [95% CI]	**RR** [95% CI]	**p-effect**	**p- heterogeneity**	**I^2** (%)	**Quality of the evidence** (GRADE)*
Myocardial ischaemia	2	8/67 (11.9)	16/66 (24.2)	9 [4-159]$^{\delta}$	0.43 [0.21-0.88]	0.02	0.84	0	Moderate +++-
PMI	2	1/67 (1.5)	4/66 (6.1)	22 [9-53]¶	0.31 [0.05-1.92]	0.21	0.86	0	Low ++--
UAP	1	1/15 (6.7)	0/11	15 [5-17]$\delta^{\P}$	2.25 [0.10-50.5]	0.61	NA	NA	Low ++--
Composite of cardiac events	2	8/67 (11.9)	13/66 (19.7)	13 [5-22]¶	0.63 [0.28-1.41]	0.26	0.90	0	Low ++--
Brady-cardia	2	3/86 (3.5)	0/85	29 [14-257]$^{\delta\P}$	7.4 [0.29-139.8]	0.18	NA	NA	Low ++--
Hypo-tension	2	3/86 (3.5)	1/85 (1.2)	44 [15-46]$^{\delta\P}$	2.21 [0.34-14.4]	0.41	0.77	NA	Low ++--
All-cause mortality	1	11/34 (32.4)	11/29 (37.9)	18 [3-6] ¶	0.85 [0.44-1.67]	0.64	NA	NA	Low ++--

* Guyatt GH, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.

$^{\delta}$ NNH: number needed to harm.

¶ CI for absolute risk reduction extends from a negative to a positive number.

Abbreviations: n/N, events/randomized patients; NNT, number needed to treat; NNH, number needed to harm; CI, confidence interval; RR, risk ratio; GRADE, GRADE Working Group grades of evidence¶; PMI, perioperative myocardial infarction; UAP, unstable angina pectoris; NA, not applicable.

At the first evaluation, there was a disagreement regarding 8 of 21 items (38.1%), mostly regarding the blinding of participants and personnel. All discrepancies were resolved in the final evaluation. None of the studies reported the incidence of AKI or composite of adverse renal events. Furthermore, regarding the adverse reactions potentially associated with beta blocker treatment, none of the studies reported the incidence of bronchospastic symptoms, neurologic sequelae, stroke, or serious infection/sepsis. E-mail enquiries to the authors confirmed that information (e.g. unpublished observations) regarding the missing outcome measures was not available.

Completeness of reported data

The calculated data completeness scores are presented in Appendix 7. Initially, there was disagreement regarding 19 of the 108 registered data items, mostly considering the reported outcome measures. All discrepancies were resolved in the final evaluation. The average total data completeness score was 19.7 (range 18 to 22) of a maximum of 38. Generally, the studies reported 55.3-57.9% of the required data; data regarding predefined outcome measures were most frequently missing. None of the studies reported the effect of esmolol on 30-day survival.

The trial sequential analysis confirmed that the detected effect of esmolol on decrease of myocardial ischemia was significant. However, the detected effect was only about 10% of the optimal information size of 1000 participants, required to detect a 20% relative change, in case that median control group event rate is assumed to be observed. Considering the other outcomes, there were no significant findings and a much larger information size would have been required.

DISCUSSION

PRINCIPAL FINDINGS

Perioperative myocardial infarction is a common complication in patients undergoing non-cardiac surgery in a Finnish tertiary care hospital, especially in patients with cardiac risk factors. The incidence of PMI in a cohort of unselected patients aged over 50 years was 7%. Patients undergoing vascular surgery were at a particularly high risk for perioperative cardiac complications, with an 11% incidence of PMI. PMI was associated with a fivefold increase in 90-day mortality. Furthermore, a mere perioperative troponin elevation without other ischemic signs or symptoms was associated with a twofold increase in 90-day mortality. Only 20% of PMI patients had ischemic symptoms, and therefore, without systematic ischemia monitoring the majority of PMIs would remain undiagnosed. The Gupta cardiac risk calculator predicted PMI, thus, the use of this index in preoperative evaluation may aid in identifying the patients with increased perioperative cardiac risk. However, the predictive ability of the index in the current cohort was substantially lower than in the development and validation cohorts in the USA (an AUC of 0.72 versus 0.88 and 0.87, respectively). The reason for suboptimal performance may be in the design of the index. The Gupta cardiac risk calculator was developed using statistical regression-based techniques that consider only a limited number of risk factors and assume a linear relationship between the risk factors and the outcome of interest. However, in practice, the risk for an adverse cardiovascular event depends upon a complex interaction between the different risk factors, and thus, the risk indices provide only a simplified and approximate risk assessment model. Furthermore, the Gupta cardiac risk calculator was developed and validated in a cohort in which PMIs were diagnosed based on clinical suspicion. Since no routine cardiac biomarker monitoring was used, this probably led to an underestimation of the number of PMIs (Bilimoria *et al.*, 2013).

Postoperative transient myocardial ischemia is a strong predictor for development of PMI. The risk for PMI increases in conjunction with increasing ischemic load. In this study, one-third of vascular surgery patients with high perioperative cardiac risk had postoperative ischemic episodes detectable by cECG monitoring. The baseline heart rate was significantly higher in patients with postoperative ischemia than in those without. Cumulative ischemic load had an excellent sensitivity in the prediction of PMI. However, IL was not associated with rising or falling troponin values, suggesting that transient, short-duration ischemic episodes are insufficient to cause myocardial injury and cardiac enzyme release. It has been demonstrated that even minor (below the upper reference limit) cardiac troponin elevations are associated with worse survival after non-cardiac surgery (Devereaux *et al.*,

2012). This study did not record changes in troponin level below the upper reference limit, and thus, it is possible that the association between transient ischemic episodes and minor troponin leakages was missed. Currently, perioperative troponin surveillance is highly advocated (Mauermann *et al.*, 2016). Whether more frequent or continuous perioperative monitoring of hemodynamic parameters, oxygenation, and ECG adds sensitivity and specificity to myocardial ischemia detection and improves postoperative outcome needs to be investigated in future trials.

The pathophysiology of PMI is not completely understood. Although the majority of patients who sustain PMI have either moderate or severe coronary artery stenoses, stable obstructive coronary artery disease does not necessarily increase the risk for perioperative cardiac complications (Sheth *et al.*, 2015). However, PMI may develop in the absence of clinically significant coronary stenoses (Sheth *et al.*, 2015). Considering the partly hereditary nature of endothelial function and its independent association with development of acute coronary syndromes, acute endothelial glycocalyx injury and subsequent dysfunction could be a critical step in determining the patients who are susceptible to PMI. Nevertheless, the current study was unable to show any association between acute endothelial injury, reflected by elevated plasma concentrations of EG markers, and PMI. However, systemic inflammation was associated with PMI. As acute inflammation is associated with maladaptive responses of the endothelial glycocalyx, (Joffre *et al.*, 2020), it is possible that the present study simply failed to demonstrate the potential endothelial injury of PMI patients, because of the inadequate power of the study. Larger studies are needed to confirm or refute these findings.

Efficacy and safety of intravenous beta blockade, titrated according to individual hemodynamic targets, for perioperative cardiac protection was investigated in a systematic review and meta-analysis. The aim of the study was to investigate the possible beneficial and harmful effects of esmolol on clinically relevant 30-day postoperative outcomes. The results showed that esmolol reduced postoperative myocardial ischemia, but its potential effect on increased bradycardia or hypotension remained unclear. However, as only few studies on short-acting intravenous beta blockade in non-cardiac surgery exist, the study was unable to determine the effects of this intervention on clinically relevant postoperative outcomes, such as mortality. The lack of the studies may be partly be due to challenges in conducting the perioperative monitoring needed to safely administer intravenous beta blockers. As shown in Study II, postoperative cumulative ischemic load was strongly associated with development of PMI and combined with heart rate and blood pressure monitoring could provide a way to safely target such treatment. Recently, several manufacturers have launched light, wireless hemodynamic monitoring devices. In the future, improved routine perioperative monitoring may enable larger clinical studies on the effects of intravenous beta blockade on clinically significant patient-centered outcomes.

INCIDENCE AND PROGNOSIS OF PERIOPERATIVE MYOCARDIAL INFARCTION IN A FINNISH TERTIARY CARE UNIVERSITY HOSPITAL

Major cardiac complications after non-cardiac surgery are common and are associated with substantial mortality and increased costs of medical care (London, 2009). The observed incidence of PMI in our Finnish single-center series corresponds with observations of other large-scale studies (Devereaux *et al.*, 2011; Devereaux *et al.*, 2008; Nagele et al., 2013; van Waes et al., 2013). One perioperative myocardial ischemic complication has been estimated to cost nearly 10 000 USD (Mackey et al., 2005), and in the context of the current results (Study I) this translates to excess costs of nearly one million euros per year in Meilahti Hospital alone. The risk for major perioperative cardiac complications varies largely between individual patients being the highest in patients undergoing vascular surgery. This is mainly due to the significant burden of cardiovascular diseases carried by many of these patients. According to a study by Hertzer et al. (1984), the proportion of vascular surgery patients with healthy coronary arteries can be as low as 8%. In the current study, 11% of the patients undergoing vascular surgery sustained PMI, which is in accordance with earlier findings (McFalls *et al.*, 2004; Borges et al., 2013). Clinical presentation of PMI is often asymptomatic, or the symptoms are non-specific. Thus, relying solely on physician-initiated ischemia monitoring will likely lead to several missed PMIs. Retrospective, register-based studies without systematic ischemia monitoring have consistently reported lower incidences of PMI than prospective trials, (Udeh *et al.*, 2014; Ghaferi *et al.*, 2009; Menendez *et al.*, 2015), probably reflecting the accuracy of clinical diagnostics of perioperative myocardial ischemia. The same observation was made in this study when comparing the cohorts with and without systematic ischemia monitoring; despite higher risk profile of the patients, TnT was measured perioperatively only in 22% of the patients without systematic ischemia monitoring and three PMIs were diagnosed.

The 90-day mortality after PMI was 29.6%. The mortality rate is high relative to previous prospective trials (Devereaux *et al.*, 2011; Devereaux *et al.*, 2012; Borges *et al.*, 2013). The majority of deaths occurred during the first 23 postoperative days, reflecting the severity of the disease. Generally, in-hospital mortality after surgery in Finland is low compared with other European countries (Pearse *et al.*, 2012). However, based on the results of the current study, perioperative cardiac complications seem to substantially worsen postoperative outcome. As the population ages and comorbidities become more common, the significance of the problem is likely to increase.

Despite overall advancements in perioperative care, PMI incidence and associated mortality have not significantly decreased in Finland during the past decades (von Knorring, 1981). To improve the prognosis, perioperative cardiac risk assessment and more intense monitoring of high-risk patients should become an integral part of perioperative care. As perioperative

myocardial ischemia is most commonly asymptomatic, routine troponin measurements should be applied. However, also useful would be identifying patients with intermediate or high cardiac risk who would actually benefit from such monitoring. Perioperative cardiac risk indices are feasible and despite their limitations, discriminate relatively well between patients with high and low cardiac risk. In the current study (I), the Gupta cardiac risk calculator predicted PMI with an AUC of 0.73 (95% CI: 0.64-0.81). The best cut-off value was 2.55 with sensitivity, specificity, and LR+ of 0.57, 0.81, and 3.01 (95% CI: 2.02-4.49), respectively. The low sensitivity may be explained by the different ischemia monitoring strategies in the current study and in the development and validation studies by Gupta and colleagues. In those studies, PMIs were diagnosed based solely on clinical suspicion, which probably has led to an underestimation of the number of PMIs. Of note, the risk index did not predict the incidence of postoperative myocardial ischemia, as also seen in Study II. Finally, if routine troponin monitoring is to be implemented into clinical practice, cooperation between cardiologists and internists needs to be strengthened to ensure so that patients with perioperative myocardial ischemia will be appropriately assessed and treated, when indicated.

SILENT PERIOPERATIVE MYOCARDIAL ISCHEMIA

The prognostic significance of postoperative myocardial ischemia, manifested by ST-segment deviation in Holter monitoring, was investigated (Study II) for the first time since studies by Landesberg and colleagues in 2000-2005. Earlier studies have demonstrated that prolonged postoperative myocardial ischemia is associated with development of cardiac complications and mortality (Frank *et al.*, 1990; Ganz *et al.*, 1994; Landesberg *et al.*, 1993; Landesberg *et al.*, 2001). However, the subject has not been investigated further, and it is unclear whether early recognition and management of this type of ischemia affect survival. In addition to investigating the prognostic significance of postoperative ischemia, this study aimed to determine the aspects necessary for feasible monitoring at the surgical ward, with the objective that continuous monitoring of hemodynamic data, oxygenation, and ECG alongside cardiac biomarker measurements could become routine in patients with high cardiac risk.

Postoperative ischemia was common; one-third of patients had ischemic episodes after undergoing peripheral arterial surgery. All the ischemic episodes were of the ST-segment depression type, and over 80% of the ischemia was asymptomatic. The cumulative ischemic load strongly predicted development of PMI with an AUC of 0.87 (95% CI: 0.75-0.99). The best cut-off value was 12.5 μVxmin, with sensitivity, specificity, and LR+ of 1.0, 0.74, and 3.83 (95% CI: 2.36-6.23), respectively. The high sensitivity implies that prognostically significant ischemia was not missed in this type of monitoring and is in accordance with earlier observations (Landesberg, 2005).

Patients sustaining PMI typically have a stable multi-vessel coronary artery disease (Biccard and Rodseth, 2010). Perioperative hemodynamic disturbances, such as tachycardia and hypotension, mental stress, and postoperative procoagulatory state may cause the stable disease to become unstable. It was observed in the current study (II) that most of the 12 ECG leads showed ischemic changes at least at some point of monitoring. Stress-induced ST-segment depression type of ischemia usually affects a substantial part of the subendocardium (Ellis *et al.*, 1996), and it is impossible to pinpoint the culprit vessel. Considering this, the more ECG leads used for postoperative ischemia monitoring, the better the ischemia detection sensitivity. However, 12-lead Holter devices are usually too complex and impractical for everyday routine use. Despite a precordial lead V5 being the most commonly used in three-lead ECG devices, V4 had a better ischemia detection sensitivity in the current study, both at the beginning of and at the peak ischemia (51.4% vs. 24.7% and 45.7 vs. 17.4%, respectively). The best ischemia detection sensitivity was acquired with the combination of leads II, aVF, V4, and V5 (97.2%). The current findings are in accordance with earlier studies (London et al., 1988; Martinez *et al.*, 2003) and support the observation that combining two precordial leads enhances ischemia detection sensitivity. Furthermore, the optimal combination for three-lead ECG should perhaps be re-evaluated.

Although a 12-lead Holter device is superior in ischemia detecting sensitivity (Landesberg, 2005), it might be too complex for routine everyday use. To be feasible for large-scale use in low-acuity setting, the monitoring device should be light, relatively small, and easy to assemble and disassemble. The number of leads should be reduced to a minimum offering adequate ischemia detection sensitivity. However, since lead detachment and artifacts are common in the use of Holter monitoring, at least two precordial leads are probably needed to ensure satisfactory sensitivity. To enable postoperative mobilization, monitoring devices should ideally be wireless. Furthermore, the monitoring data should be available on a daily basis and an alarm should be triggered by ischemia. Studies have shown that asymptomatic ischemia often occurs prior to myocardial injury, reflected by cardiac biomarker release (Frank *et al.,* 1990; Landesberg *et al.*, 1993; Landesberg *et al.*, 2001), and timely detection and management of ischemia would prevent further, potentially more serious complications.

As postural changes are the most common reason for false-positive ischemic alarms, (Adams and Drew, 2002), an integrated motion sensor would improve the accuracy of ST-segment analysis. This was tested in the current study (II); however, a correlation between specific posture and ST-segment deviation could not been found. Moreover, postural changes did not trigger false alarms. However, the algorithm was tested with only with a very small number of patients, and thus, the result needs to be re-tested and validated in a larger cohort.

SYSTEMATIC ISCHEMIA MONITORING VS. ROUTINE CLINICAL PRACTICE

Without systematic perioperative ischemia monitoring the majority of perioperative cardiac complications will go undiagnosed. As discussed earlier in this section, register-based studies without systematic measurements of cardiac biomarkers report approximately three to five times lower incidence rates of PMI than prospective studies. Many physicians thus seem to be unaware of the high incidence and poor prognosis of perioperative myocardial ischemia and, perhaps more importantly, have been reluctant to screen it since treatment recommendations or guidelines have not been available. This study demonstrated that physicians seldom order perioperative troponin measurements, even in high cardiac risk patients (Study I). In the cohort with routine perioperative care, troponins were measured in only 39 patients (22%), three (1.7%) of whom sustained PMI. The patients underwent more urgent or emergency operations and had a higher 90-day mortality (13.1% vs. 7.3%) than patients with systematic ischemia screening. Accordingly, it is likely that many perioperative cardiac complications were missed in these patients. Furthermore, performing a study may improve the diagnostics and treatment of similar patients not enrolled in the study (Hawthorne effect). As the participants of the study were treated at the same wards by the same physicians, it may be assumed that their monitoring affected the treatment of other patients as well. Thus, without the study, probably more PMIs would have been missed by physician-initiated ischemia monitoring, and the true advantage of systematic ischemia screening might be larger than that observed.

To screen a disease, the used screening method applied should be able to discriminate high-risk patients, be validated in prospective studies examining hard patient-centered outcomes, exhibit incremental value, be of clinical utility and improve clinical outcomes. The last point has yet to been shown in routine perioperative cardiac biomarker, namely troponin, screening. Because of uncertainty with regard to modification of clinical outcomes, opinions on perioperative ischemia monitoring differ. According to some expert opinions, troponin should be measured both preoperatively and 48-72 hours after major surgery in high-risk patients (Kristensen *et al.*, 2014; Thygesen *et al.*, 2012). By contrast, the ACC/AHA guidelines state that the usefulness of perioperative troponin screening is uncertain, as recommendations on management are lacking (Class IIb, Level B) or only recommend measuring troponin if signs or symptoms suggestive of myocardial ischemia are present (Fleisher *et al.*, 2014). This approach, however, completely dismisses MINS and its prognostic significance. The data regarding medical therapy after PMI or MINS are somewhat inconclusive. Foucrier and colleagues showed in 2014 that patients with perioperative troponin elevation not receiving intensification of cardiovascular medical therapy had higher risk for long-term mortality and cardiovascular complications than patients whose

medical therapy was intensified (Foucrier *et al.*, 2014). However, in a study by Chong and colleagues, cardiology care and medical therapy intensification after perioperative troponin elevation did not reduce one-year mortality or cardiovascular complications (Chong *et al.*, 2012). The problem with routine perioperative troponin screening seems to be its inability to differentiate between cardiac and non-cardiac causes. It has been shown that even minor troponin elevations are associated with worse postoperative outcome (Devereaux *et al.*, 2012), and, for example, in the MANAGE trial this has been an indication to initiate dabigatran (Devereaux *et al.*, 2018). Although dabigatran reduced long-term major vascular complications, it did not reduce myocardial infarction or all-cause mortality per se. Furthermore, although not life-threatening, dabigatran caused some considerable bleeding problems (Devereaux *et al.*, 2018). Accordingly, the heterogeneity among the results of medical therapy intensification after MINS may be at least partly due to the issue that intervention has been targeted to patients who actually do not need it or may even be harmed by it.

Despite both MINS and PMI being associated with substantial mortality, only few operative units have perioperative troponin monitoring as a routine clinical practice. In fact, reluctance exists in measuring troponin in surgical patients, most likely because interpretation of slightly elevated values is challenging, and it is still unclear whether the benefit of treatment is as marked as in non-operative AMI. However, without perioperative ischemia monitoring we will miss approximately 60% to 80% of PMIs and up to 90% of MINSs. While looking solely at the costs of perioperative troponin monitoring, Buse and colleagues estimated the incremental cost of avoiding missing a MINS event as 1632 CAD (2015 Canadian dollars). The cost-effectiveness of troponin monitoring was higher in patients with increased cardiac risk, the incremental cost being 1309 CAD (Buse *et al.*, 2018). By comparison, cost of avoiding a breast or cervical cancer thanks to screening is over 10-fold (14 396 CAD and 18 176 CAD, respectively) (Devereaux and Szczeklik, 2019). Finally, the most important goal of perioperative ischemia monitoring is to reduce postoperative morbidity and mortality. As the Western population is rapidly ageing, prevention, detection, and treatment of perioperative cardiac complications is more relevant than ever. Given that the vast majority of prognostically important myocardial ischemia and infarctions will go undetected without troponin monitoring and the outcome may be modifiable with interventions, perioperative ischemia monitoring should be conducted for patients with cardiac risk factors undergoing major surgery. Combining pre-existing comorbidities with intraoperative adverse events may improve the prognostic value of postoperative troponin monitoring.

In conclusion, patients with high cardiac risk would probably benefit from perioperative troponin screening. For these patients, troponin should be measured both preoperatively and after surgery to differentiate perioperative myocardial injuries from chronic troponin elevations. Patients with MINS or PMI would perhaps benefit from medical interventions; however, these

should be initiated only after cardiologic assessment of benefits and risks. Finally, cardiac biomarker screening in low-risk patients is not useful since perioperative mortality in this group is quite limited (Beattie *et al.*, 2012).

ROLE OF ENDOTHELIAL GLYCOCALYX INJURY AND SYSTEMIC INFLAMMATION IN PERIOPERATIVE CARDIAC COMPLICATIONS

The pathophysiology of perioperative myocardial injury is not completely understood. Clean coronary arteries do not necessarily protect from the complication, and, on the other hand, patients with severe coronary artery disease may undergo a major surgery without any problems (Sheth *et al.*, 2015). Elucidating the pathophysiological mechanisms of perioperative myocardial ischemia would enable better preoperative risk stratification of patients and development of more efficient and safer prevention and treatment methods. Considering the systemic nature of endothelial dysfunction and its central role in the pathogenesis of atherosclerosis, it seems logical that endothelial injury would be associated with development of perioperative cardiac complications as well. Furthermore, many factors associated with major surgery, such as ischemia-reperfusion, inflammation, and fluid overload, damage the endothelial glycocalyx. Rhem and colleagues showed in 2007 that endothelial glycocalyx injury may occur after major aortic surgery, causing the components of the glycocalyx to leak into circulation. Moreover, using an animal model the authors demonstrated that the plasma-measurable components of glycocalyx (syndecan-1 and heparan sulfate) originated from coronary vessels (Rhem *et al.*, 2007). Based on these findings and the known association of endothelial dysfunction with acute, nonoperative coronary syndromes, (Bonetti *et al.*, 2003; Gokce, 2011; Suwaidi *et al.*, 2000), this study (III) aimed to investigate the association of acute systemic inflammation and endothelial injury with PMI. The results showed that systemic inflammation, reflected by high IL-6 plasma levels, was associated with PMI. Furthermore, the highest value of IL-6 predicted PMI with an AUC (95% CI) of 0.69 (0.54-0.85), (p=0.02). The best cut-off value for IL-6 was 0.24 pg/L with sensitivity, specificity, and positive and negative likelihood ratios (95% CI) of 0.53, 0.85, 3.56 (1.65-7.65), and 0.55 (0.32-0.95), respectively. None of the measured components of the glycocalyx (sTM, syndecan-1, and VAP-1) were predictive of PMI. However, in PMI patients 24-hour postoperative sTM correlated positively with preoperative and 6- and 24-hour postoperative TnT (p=0.05). Currently, there are no other reports on the role of endothelial dysfunction in the development of cardiac complications in non-cardiac surgery. With regard to a nonoperative setting, high plasma levels of sTM have been shown to be associated with acute ST-segment elevation myocardial infarction (STEMI), and in the same patients, high syndecan-1 levels were associated with heart failure and short- and long-term mortality (Ostrowski et al., 2013).

Furthermore, Bro-Jeppesen and colleagues demonstrated that sustained EG injury is related to the severity of post-cardiac arrest syndrome and baseline IL-6 levels were correlated with EG activation and endothelial cell injury in patients with severe myocardial damage (Bro-Jeppesen *et al.*, 2016).

Several explanations for the inconclusive findings of the current study may be suggested. First, the study was relatively small. Because of the statistical methods applied, 12 PMI patients had to be excluded from the analyses. If mixed model analysis had been used, six of these patients, with only 6-hour postoperative or 24-hour postoperative samples missing each, could have been included, thus increasing the statistical power of the study. Second, it is possible that the timepoints of EG marker measurement were not adequate to cover the true perioperative kinetics of the markers. The markers were chosen to be measured preoperatively and at 6 hours and 24 hours postoperatively to investigate the direct effect of surgery on endothelial function. However, it is possible that perioperative endothelial injury occurs later than this. Finally, it is possible that circulating plasma components of the endothelial glycocalyx do not fully reflect the integrity of the coronary endothelium, and the FMD test, for instance, might have been better suited for this purpose. Some evidence suggests that endothelial function is modifiable. A small study by Manchurov and colleagues showed that remote ischemic preconditioning (RIPC) before pPCI clearly improved endothelial function in patients with acute myocardial infarction (Manchurov *et al.*, 2014). To better understand the pathophysiology of PMI and to possibly find methods for perioperative cardiac protection by affecting the integrity of endothelium, further investigation on the association of endothelial glycocalyx injury with PMI is warranted. The current findings should be considered as first hypothesis-generating preliminary evidence that needs to be re-evaluated in future larger studies.

ROLE OF ESMOLOL IN PERIOPERATIVE CARDIAC PROTECTION

According to current evidence, the adverse effects of perioperatively started oral beta blockers overshadow their benefit in reducing myocardial ischemia (Wijeysundera *et al.*, 2014). An alternative is offered by using drugs with short half-life and with the ability to be titrated according to individual hemodynamic targets. Esmolol is an ultra-short-acting beta blocker with a plasma half-life of two minutes and a washout time of approximately nine minutes after stopping infusion (Fita *et al.*, 1999). Because of these properties, esmolol seems suitable for prevention of myocardial ischemia in the perioperative period, when it is sometimes, for example, in the case of bleeding, necessary to immediately interrupt the administration of the drug. A couple of small, underpowered randomized controlled trials have investigated the efficacy of esmolol for perioperative cardiac protection (Raby *et al.*, 1999; Urban *et al.*, 2000). Furthermore, in 2010, Landoni and

colleagues conducted a systematic review and meta-analysis to determine the clinical impact of esmolol on patients undergoing non-cardiac surgery (Landoni *et al.*, 2010), and in the following year, Yu and colleagues revisited this subject with a meta-analysis including more studies (Yu *et al.*, 2011). These previous studies demonstrated that esmolol seems to reduce myocardial ischemia, and the adverse effects, namely bradycardia and hypotension, can be reduced when the drug is given as a continuous infusion (Landoni *et al.*, 2010; Yu *et al.*, 2011). However, data regarding the effect of esmolol on patient-centered outcomes, such as mortality, and on non-cardiac organs are limited. This study aimed to investigate these subjects by means of a systematic review and meta-analysis. Compared with the earlier studies, only studies reporting postoperative follow-ups and outcomes were included. The number of eligible studies and the number of patients included in these studies was low causing the meta-analysis to be inadequate in statistical power. TSA analysis confirmed this for all the outcomes. According to the results, esmolol seemed to reduce myocardial ischemia, but its effect on major postoperative cardiac and non-cardiac complications, such as PMI, AKI, or stroke, and mortality remains unclear. Furthermore, the potential association of esmolol with increased bradycardia and hypotension could not be confirmed or refuted. The earlier studies were able to investigate this question with a larger statistical power, as the meta-analyses also included studies with only intraoperative esmolol administration and follow-up, thus having a much larger number of eligible studies (3 vs. 32 vs. 67). In both of the earlier meta-analyses, the majority of the included studies investigated the effect of esmolol on controlling the hemodynamic responses associated with laryngoscopy and endotracheal intubation and included rather healthy patients. Landoni and colleagues concluded that esmolol did not increase episodes of bradycardia and hypotension (Landoni *et al.*, 2010). However, the study by Yu and colleagues showed that esmolol was associated with an increase in incidence of unplanned hypotension, especially when administered in larger bolus doses (Yu *et al.*, 2011). The potential cardioprotective effects of esmolol are likely to be acquired with a small initial dose and a continuous infusion, and esmolol has the potential to be both effective and safe in the prevention of perioperative myocardial ischemia. However, randomized controlled trials with higher risk patients, longer duration infusions, and with adequate postoperative follow-up are needed to determine the efficacy and safety of esmolol in perioperative cardiac protection.

LIMITATIONS

This study has some important limitations that should be considered when interpreting the results.

First, this was a single-center study and the vast majority of the patients underwent surgery in general anesthesia. Therefore, the results are not necessarily generalizable to all Finnish surgical patients, and the effect of anesthetic technique (general vs. neuraxial anesthesia) on myocardial ischemia could not be investigated.

Despite the research group working outside hours and treating physicians also participating in the recruitment of patients, the planned 24/7 recruitment coverage was not attained in Study I. To make the cohort more representative, routinely collected clinical data of patients whose consent was missed during the recruitment and who did not decline the use of their data, were analyzed and compared with the data of the patients with systematic ischemia monitoring. With this approach, the challenges with recruitment offered an opportunity to compare the postoperative outcome of patients receiving systematic ischemia screening with the outcome of patients receiving standard care. Due to differences in recruitment and data collection the comparison of the two groups remained descriptive.

The aim of Study II was to investigate the feasibility of continuous Holter monitoring in detecting postoperative myocardial ischemia and the ability of cumulative ischemic load in predicting PMI. Due to the small number of patients, the study was, however, statistically underpowered to build a model that would support the use of a cumulative IL as an automated ischemia alarm. Furthermore, Holter monitoring was initiated only after the surgery, and it is therefore possible that prognostically important pre- and intraoperative events were missed.

The limitations of Study I affect the results of the laboratory substudy (III) as well. Furthermore, because of the statistical methods applied, 12 PMI patients with missing blood samples had to be excluded, decreasing the statistical power of Study II. Secondly, the observational design of Study II does not allow an evaluation of the causal relationship. The findings should merely be considered as hypothesis-generating preliminary evidence regarding the potential association of endothelial glycocalyx injury with PMI, requiring larger studies to confirm or refute them.

Finally, because of the low number of eligible studies and the small number of patients included, the statistical power of the systematic review and meta-analysis (IV) was inadequate, as confirmed by TSA analysis. Furthermore, the review included studies comparing esmolol with placebo and studies comparing esmolol with another drug. This approach may have affected the results of the meta-analysis. According to the results of Study IV as well as the results of the earlier studies (Landoni et al., 2010; Yu *et al.*, 2011), intravenous esmolol seems promising in the prevention of myocardial ischemia. Whether this intervention is safe and has an impact on postoperative outcome requires investigation in adequately powered trials.

FUTURE IMPLICATIONS

According to the findings of Studies I-IV, perioperative cardiac complications are common in patients aged over 50 years, especially if they have pre-existing cardiovascular morbidity, and are associated with a fivefold increase in 90-day mortality. Increasing evidence suggest that dismal prognosis of PMI may be modifiable by, for example, by intensification of cardiovascular medication or antiplatelet therapy, and this speaks in favour of routine perioperative ischemia screening. However, the screening of patients with low cardiac risk is not useful. Cardiac risk assessment should be an integral part of preoperative evaluation, and the use of perioperative cardiac risk indices and functional capacity indices (i.e. Duke activity status index) may add to the accuracy of clinical assessment. Routine cardiology consultation may be beneficial for patients with cardiac risk factors (Squizzato *et al.*, 2020). Additionally, clinical tests, namely cardiac stress test, can help to differentiate between intermediate and high-risk patients (Augoustides *et al.*, 2013).

In addition to the conventional risk factor assessment, in the future we may be able to estimate patients' cardiac risk at the cellular or molecular level. Atherosclerosis is an inflammatory disease and endothelial dysfunction plays a central role in the process. Furthermore, endothelial dysfunction is associated with the development of atherosclerotic complications (Bonetti *et al.*, 2003). The association of an acute endothelial dysfunction with PMI was investigated in this thesis, and although the results were inconclusive, soluble thrombomodulin correlated with perioperative TnT indicating that the subject should be investigated in future larger trials. Contrary to endothelial markers, a perioperative rise of interleukin-6 was associated with development of PMI, reflecting the inflammatory nature of the disease. In accordance with this observation, Handke and colleagues recently published a study where they demonstrated a perioperative rise of the monocyte activation marker presepsin in patients who had sustained cardiovascular death, MI, myocardial ischemia, or stroke (MACCE) during the first 30 days after non-cardiac surgery. Furthermore, the authors demonstrated that preoperatively elevated presepsin predicted MACCE after surgery and even improved BNP-based risk stratification (Handke *et al.*, 2019). Although the study was small and has some limitations, it supports the hypothesis that preoperative inflammatory status might play a causative role in perioperative cardiovascular events and modulation of this could comprise a new target for prevention.

In the recent years, there has been a major change in the definition of perioperative cardiac complications. After several publications emerged from the VISION cohort, (Devereaux *et al.*, 2012), a shift in terminology from PMI to MINS has occurred. In 2018, MINS was established as a diagnosis in the fourth definition of myocardial infarction in the European Society of Cardiology clinical practice guidelines. Despite the clear established linkage between postoperative cardiac troponin elevations and increased mortality,

it is important to note that postoperative troponin elevations can be due to various etiologies, some of which are non-ischemic, such as sepsis or chronic kidney disease. Furthermore, a large proportion of high-risk surgical patients have preoperatively elevated troponin levels (Nagele *et al.*, 2013). Even in diseases originating outside the heart, elevated troponin has been linked to poorer outcome (Martins *et al.*, 2018; John *et al.*, 2010). Without knowledge of preoperative baseline value, postoperative troponin elevation is merely a non-specific marker of hazard, as suggested by Beckman (2013). Currently, clinical practices regarding the timing of perioperative troponin measurement vary markedly, and this might have affected the results of some trials attempting to find treatments for MINS, e.g. the MANAGE trial. As no preoperative troponin measurement was required in the trial and the benefit of dabigatran following MINS appeared to be mainly due to a reduction in non-hemorrhagic stroke, it is possible that at least a subset of patients had non-ischemic myocardial injury and troponin elevation (Devereaux *et al.*, 2018). However, the authors succeeded in introducing a new intriguing strategy to improve the postoperative outcome of a large and previously neglected group of patients and the study opens the door for further investigations. Regarding prevention of MINS, Ekeloef and colleagues recently published an interesting report on the effect of remote ischemic preconditioning on myocardial injury in emergency hip fracture surgery (Ekeloef *et al.*, 2019). The authors showed that RIPC reduced the risk of perioperative myocardial injury and infarction in a cohort of 648 patients with cardiovascular risk factors. The study was too underpowered to draw conclusions on several clinically important outcome measures, such as 30-day mortality, and the results of the long-term effect of RIPC are not yet available. RIPC seems an attractive option for perioperative cardiac protection as it is inexpensive and clinically applicable and has very few clinically significant side-effects (Hausenloy *et al.*, 2015). However, prior to a change in practice, future larger studies are needed to elaborate the effect of RIPC on cardiovascular and other clinically important outcomes after non-cardiac surgery. Despite promising preliminary findings, recent large studies investigating the effect of RIPC in cardiac surgery have not found any effect on clinical outcomes, including myocardial infarction and mortality (Hausenloy *et al.*, 2015; Hausenloy *et al.*, 2007; Meybohm *et al.*, 2015).

Regarding medications, perioperative statin therapy seems to be beneficial in preventing cardiac complications in non-cardiac surgery, perhaps due to its endothelial stabilization properties (Putzu *et al.* 2018). The recently updated ESC/EAS guidelines for the management of dyslipidemias recommend an LDL-cholesterol reduction of ≥ 50% from baseline and an LDL-cholesterol goal of < 1.4 mmol/L in secondary prevention for patients at very high cardiovascular risk (Mach *et al.*, 2020). However, in real-world clinical practice, this ambitious goal may be hard to achieve (Dykun *et al.*, 2020). Recently, a new class of lipid-lowering drugs, PCSK9 inhibitors, has become available. These drugs are extremely efficient in reducing LDL-cholesterol levels and

may reduce cardiovascular events in line with the LDL-cholesterol reduction achieved (Mach *et al.*, 2020). However, considering the costs of PCSK9 inhibitor treatment and the lack of data on long-term safety, the drugs are not yet in everyday use (Mach *et al.*, 2020). Evidence regarding other cardiovascular medications is inconclusive and mostly limited to risk-adjusted observational studies. However, recently some large RCTs have demonstrated that surgical patients with a high cardiac risk may benefit from anticoagulant therapy, alone or combined with aspirin (Devereaux *et al.*, 2018; Bonaca *et al.* 2020). Clinicians may consider initiating treatment with of angiotensin-converting enzyme inhibitor, antiplatelet and/or anticoagulant, or beta blocker based on individual assessment. Beta blockers should not be started preoperatively for beta blocker-naïve patients without careful titration of the dose according to heart rate and blood pressure. Especially when dual-pathway inhibition is considered, benefits of the treatment should be weighed against the risk of bleeding. Finally, if patients with MINS or PMI demonstrate recurrent instability, coronary angiography should be considered. Again, the potential benefit of the procedure should be weighed against the risk of bleeding.

Taken together, while ongoing research is trying to find interventions to prevent MINS and PMI and to improve the outcome of patients sustaining these complications, the management of MINS and PMI should be based on the best clinical practices available today. First, we should preoperatively recognize the high-risk patients. In the future, we might be able to use information on patients' genetic background, glycocalyx integrity or inflammatory status, but in the meantime, assessment should be based on clinical cardiovascular risk factors. Perioperative troponin measurements should be considered for patients deemed at high risk preoperatively and undergoing major surgery. It is important to measure the preoperative troponin value in order to be able to distinguish chronic troponin elevations from acute myocardial injuries. However, as discussed earlier, preoperative assessment of risk can be very different from postoperative likelihood of developing MINS or PMI, and incorporating assessment of intraoperative events, namely clinically significant tachycardia and/or hypotension, may add value to postoperative troponin monitoring. In terms of preventing perioperative cardiac complications, accurate monitoring of intra- and postoperative hemodynamics and treatment of hypotension, tachycardia, hypoxia, and hypothermia is effective. Moreover, low nadir hemoglobin value associated with development of PMI in the patient material of this thesis, emphasizes the importance of preoperative anemia identification and correction and also avoidance of excess blood loss during surgery. Patients who sustain MINS or PMI should be referred for cardiology consultation, and based on individual assessment cardiovascular medication should be started or intensified.

CONCLUSIONS

1. Perioperative myocardial infarction is a frequent and serious complication (7% incidence, 30% 90-day mortality) in patients aged 50 years or older undergoing non-cardiac surgery in a Finnish tertiary care hospital. Elderly patients with pre-existing cardiovascular diseases are at highest risk for developing the complication. The performance of the Gupta cardiac risk calculator was fair, and its routine use may help to identify patients benefiting from perioperative ischemia monitoring.

2. Asymptomatic postoperative ischemic electrocardiographic changes are common in high-risk patients undergoing vascular surgery and cumulative ischemic load strongly predicts development of myocardial infarction.

3. Systemic inflammation, reflected by interleukin-6, is associated with postoperative troponin release and myocardial infarction. The potential association of endothelial glycocalyx injury with perioperative myocardial infarction remains unclear, as Study III was too underpowered to answer to this question.

4. According to the systematic review and meta-analysis, intravenous esmolol, titrated according to individual heart rate and blood pressure levels, seems to reduce perioperative myocardial ischemia. The published studies were too few and too small to determine the safety of this intervention and whether it has an impact on clinically relevant, patient-centered outcomes.

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Appendix 1.
STROBE Statement – Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the design of the study with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment. Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed
		(e) Describe any sensitivity analyses

Appendix 1.
STROBE Statement – Checklist of items that should be included in reports of cohort studies

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarize follow-up time (e.g. average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done–e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	summarize key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	21	Discuss the generalizability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix 2.
Search criteria for the studies.

Combined: OR		Combined: OR		Combined: OR
Esmolol		Perioperative		Acute coronary syndrome
Adrenergic beta receptor antagonists		Postoperative		Unstable angina
Adrenergic beta-1 receptor antagonists		Intraoperative		Myocardial ischemia
Adrenergic beta-2 receptor antagonists		Surgical procedures		Myocardial injury
		General surgery		Troponin elevation
		Non-cardiac surgery		Troponin T elevation
		Noncardiac surgery		Troponin I elevation
		Vascular surgery		Arrhythmia
		Gastrointestinal surgery		Silent myocardial ischemia
		Orthopedic surgery		Myocardial infarction
		Thoracic surgery		Major adverse cardiac effects
		Obstetric surgery		Non-fatal cardiac arrest
	AND	Gynecologic surgery	AND	Cardiac death
		Urologic surgery		Congestive heart failure
		Oncologic surgery		Bradycardia
		Surgery		Tachycardia
				Hypotension
				Hypertension
				Stroke
				Mortality
				Sepsis
				Acute kidney injury
				Renal replacement therapy
				Chronic kidney failure
				Renal failure

Appendix 3.
Selection criteria for the studies

	Selection criteria
Study type	(a) Randomized controlled trial
	(b) Duplicates excluded
Date of publication	No restrictions
Language of publication	No restrictions
Setting	Operative
Type of surgery	Non-cardiac
Participants	(a) Human
	(b) Aged over 18 years
Intervention(s)/ exposure(s)	Perioperative intravenous esmolol of any dose, titration and duration
Comparator(s)/control	(a) Placebo
	(b) No treatment
	(c) Treatment with oral beta blockers/ any other medication, started perioperatively
Primary outcome(s)	Postoperative
	(a) Myocardial infarction
	(b) Myocardial ischemia
	(c) Cardiac arrest
	(d) Cardiac death
	(e) Heart failure
	(f) Unstable angina pectoris
	(g) New-onset arrhythmias
	(h) Acute kidney injury
	(i) Composite of renal events*
	(j) Composite of cardiac events$^{\delta}$
Secondary outcome(s)	(a) Clinically significant bradycardia and/or hypotension
	(b) Bronchospasm
	(c) Stroke
	(d) Neurologic symptoms
	(e) Serious infection/sepsis
	(f) All-cause mortality

* Acute kidney injury, need for renal replacement therapy or worsening/development of chronic kidney failure

$^{\delta}$ Myocardial infarction, unstable angina pectoris, heart failure, new-onset arrhythmias, cardiac death

Appendix 4.
*Summary of the RCTs reporting intraoperative data on the effect of esmolol in non-cardiac surgery***.**

Atlee JL et al.

Title: The use of esmolol, nicardipine, or their combination to blunt hemodynamic changes after laryngoscopy and tracheal intubation

Journal: Anesthesia & Analgesia

Year: 2000

Purpose of the study: To test if esmolol, nicardipine, or their combination was effective and safe in blunting an undesirable increase in heart rate (HR) and blood pressure (BP) after laryngoscopy and tracheal intubation (LTI).

Design: Open-label randomized controlled study (RCT)

Patients: 137 adult American Society of Anesthesiologists (ASA) I-III classified patients undergoing non-specified non-cardiac surgery under general anesthesia.

Intervention: Pretreatment with a single dose of esmolol 1mg/kg before induction of anesthesia (38 patients).

Control: Pretreatment with a single dose of (1) nicardipine 30µg/kg (31 patients) (2) combination of esmolol 0.5mg/kg and nicardipine 15 µg/kg (33 patients) (3) no pretreatment (35 patients).

Intraoperative outcome(s): Peak HR and BP after LTI of all the pretreatment groups were compared with the no pretreatment-group. Potential hypotension, bradycardia, tachycardia, and arrhythmias were recorded during a five-minute period.

Results: Peak HR increased after LTI in all the groups, neither of the pretreatment groups differed from the no pretreatment group. The combination of esmolol and nicardipine prevented increase in BP after LTI compared with no pretreatment. No patient was treated for hypotension, bradycardia or tachycardia. The groups were similar in terms of occurrence of arrhythmias. No serious arrhythmias occurred.

Gold MI et al.

Gold MI et al.

Title: Use of esmolol during anesthesia to treat tachycardia and hypertension

Journal: Anesthesia & Analgesia

Year: 1989

Purpose of the study: To study whether intravenous bolus-administered esmolol can be effective in the treatment of intraoperative tachycardia and hypertension.

Design: Double-blind RCT

Patients: 30 adult ASA II-III classified patients undergoing non-cardiac general surgery under general anesthesia.

Intervention: Esmolol infusion (10 mg/ml) if HR exceeded 95 bpm or SBP was greater than 140 mmHg at any point during anesthesia after induction. Loading dose was 80 mg and the infusion 12 mg/min. Nonresponders with severe hemodynamic alterations were treated with intravenous opioid or deeper volatile anesthesia.

Control: Saline bolus and infusion with the same regimen as in the intervention group (15 patients)

Appendix 4.
Summary of the RCTs reporting intraoperative data on the effect of esmolol in non-cardiac surgery.

Intraoperative outcome(s): The hemodynamic target was to decrease the initial HR or SBP at least 15%. HR and BP were measured every minute for 3 minutes after initiation of the treatment/placebo infusion. Thereafter, HR was measured every 5 minutes and BP every minute. After cessation of the infusions, BP and HR were recorded at 5-minute intervals for 30 minutes. *Result(s):* HR decreased significantly in the esmolol group, whereas placebo had no such effect. The changes in BP did not differ between the study groups.
Jangra K et al.
Title: Comparison of quality of the surgical field after controlled hypotension using esmolol and magnesium sulfate during endoscopic sinus surgery *Journal:* Journal of Anaesthesiology and Clinical Pharmacology *Year:* 2016 *Purpose of the study:* The effect of esmolol, magnesium sulfate and placebo was studied to achieve controlled hypotension and better quality of the surgical field. *Design:* Double-blind RCT *Patients:* Thirty adult ASA I-II physical status patients scheduled for endoscopic sinus surgery (ESS). *Intervention:* After induction, the treatment group received an iv-esmolol bolus of 500 µg/kg/min over 10 minutes followed by an infusion of 100-300 µg/kg/min. The target was to achieve a mean arterial pressure (MAP) of 55-65 mmHg. *Control:* Magnesium group received an iv-bolus of 10% magnesium sulfate in 10 minutes before anesthesia induction, followed by an infusion of 15-30 µg/kg/h. The MAP target was similar to the treatment group. Saline group received the same volume of placebo and the BP target was ±10% of baseline pressure. Hemodynamic alterations were treated with opioids, deepening of the anesthesia of fluid administration. *Intraoperative outcome(s):* MAP and HR were recorded at 5-minute intervals for 95 minutes. The surgical field was subjectively assessed on a 6-point scale by the surgeon. *Result(s):* Compared to control group, controlled hypotension was effectively achieved with both esmolol and magnesium. Both study drugs offered an ideal quality of the surgical field.
Kanitz DD et al.
Title: Intraoperative use of bolus doses of esmolol to treat tachycardia *Journal:* Journal of Clinical Anesthesia *Year:* 1990 *Purpose of the study:* To test the effectivity and safety of 2 different bolus doses of esmolol to treat intraoperative tachycardia *Design:* Double-blind RCT *Patients:* Forty-eight adult ASA II-IV classified patients undergoing non-cardiac general surgery under general anesthesia.

Appendix 4.
*Summary of the RCTs reporting intraoperative data on the effect of esmolol in non-cardiac surgery***.**

Intervention: Injection of either 50 mg (16 patients) or 100 mg (16 patients) of esmolol if the following prerequisites were met: SBP ≥ 110 mmHg at ≥ 20 minutes from start of maintenance anesthesia and 20 minutes before the cessation of general anesthesia. Furthermore, two sets of vital sign measurements over 1 minute had to show a HR ≥ 95 beats/min or at least a 20% increase in HR compared to the post-induction average.

Control: Placebo according to the regimen described above.

Intraoperative outcome(s): HR and BP recordings every 30 or 60 seconds for 10 minutes, respectively. During that period, anesthetic agents were administered only if 1. HR was < 50 beats/min or > 120 beats/min, 2. SBP was < 90 mmHg or > 160 mmHg and/or 3. Ischemic changes were detected on the EKG.

Results: As compared to the placebo, both esmolol doses significantly reduced the HR. Adverse effects were few.

Kol IO et al.

Title: Controlled hypotension with desflurane combined with esmolol or dexmedetomidine during tympanoplasty in adults: A double blind, randomized, controlled trial

Journal: Current therapeutic research, clinical and experimental

Year: 2009

Purpose of the study: To study the effects of dexmedetomidine or esmolol on blood loss, recovery time and tolerability during tympanoplasty under desflurane anesthesia.

Design: Double-blind RCT

Patients: Forty-eight 18 to 60-year old ASA II-IV classified patients undergoing tympanoplasty under general anesthesia.

Intervention: After endotracheal intubation, a loading dose of esmolol at 1 mg/kg over 1 minute, followed by an infusion of 0.4 to 0.8 mg/kg/h to maintain a MAP between 65 and 75 mmHg.

Control: After endotracheal intubation, a loading dose of dexmedetomidine at 1 µg/kg over 1 minute, followed by an infusion of 0.4 to 0.8 µg/kg/h to maintain a MAP between 65 and 75 mmHg.

Intraoperative outcome(s): The amount of bleeding in the surgical field was assessed on a 6-point scale (Fromme et al.*). Extubation time and recovery time (Aldrete score ≥ 9/10 [a scale of consciousness, activity, respiration, circulation, and oxygen saturation by pulse oximetry]) were recorded. In addition, a sedation score was measured at 15, 30, and 60 minutes after extubation.

Result(s): Controlled hypotension and satisfactory surgical field were achieved with both esmolol and dexmedetomidine. Both agents proved well tolerated.

Korpinen R et al.

Title: Effect of esmolol on the heart rate, arterial pressure and the electrocardiographic changes during laryngomicroscopy

Journal: Acta Anaesthesiologica Scandinavica

Year: 1997

Appendix 4.
Summary of the RCTs reporting intraoperative data on the effect of esmolol in non-cardiac surgery.

Purpose of the study: To test whether esmolol would be effective in controlling the hemodynamic effects of laryngomicroscopy.

Design: Double-blind RCT

Patients: Forty adult ASA I-II classified patients undergoing laryngomicroscopy under general anesthesia.

Intervention: A bolus dose of esmolol 1mg/kg followed by an infusion of 200 microg/kg/min (20 patients)

Control: Saline bolus and infusion with the same regimen as in the intervention group (20 patients)

Intraoperative outcome(s): Repeated heart rate and arterial blood pressure measurements with a sphygmomanometer, QRS, ST and QTc interval measurements with a signal processing method at similar time points. Last measurements were carried out when the laryngomicroscope was removed.

Results: Heart rate and QTc interval did not increase significantly during the study period as compared with baseline values, with the exception of QTc interval prolonging after cardiac intubation. Arterial pressure was increased in both groups after insertion of the operation laryngoscope. No cardiac arrhythmias occurred.

Louizos A et al.

Title: Administration of esmolol in microlaryngeal surgery for blunting the hemodynamic response during laryngoscopy and tracheal intubation in cigarette smokers

Journal: Annals of Otology, Rhinology and Laryngology

Year: 2007

Purpose of the study: To investigate the dose-response and side effects of esmolol for reducing the hemodynamic response to laryngoscopy and tracheal intubation.

Design: Double-blind RCT

Patients: 165 adult ASA I-III-classified patients undergoing elective microlaryngeal surgery under general anesthesia.

Intervention: A bolus dose of esmolol 1 mg/kg (group E1) or 2 mg/kg (group E2) during induction of anesthesia.

Control: Sodium chloride 0.9% 30 ml during anesthesia induction.

Intraoperative outcome(s): Systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) were recorded before induction of anesthesia (baseline), every minute for 5 minutes after intubation and every 3 minutes for the rest of the surgical procedure.

Results: In the group E2, no significant hemodynamic fluctuations were detected after intubation. In the placebo and E1 groups significant alterations in cardiovascular parameters were detected in the first 3 minutes (placebo) and first 2 minutes (E1) after tracheal intubation. In the placebo group, the alterations persisted during surgery.

Appendix 4.
*Summary of the RCTs reporting intraoperative data on the effect of esmolol in non-cardiac surgery***.**

Miller RD et al.

Title: Bolus administration of esmolol for controlling the hemodynamic response to tracheal intubation: the Canadian multicenter trial

Journal: Canadian Journal of Anaesthesia

Year: 1991

Purpose of the study: To study the dose-response and side effects of esmolol administered before the induction of anesthesia for blunting the hemodynamic response to intubation.

Design: Multicenter double-blind RCT

Patients: 548 adult ASA I-IV-classified patients from 12 university-affiliated centers undergoing non-cardiac surgery under general anesthesia.

Intervention: Esmolol 100 mg (group E100) or 200 mg (group E200) as a 10 ml bolus injection during the anesthesia induction.

Control: Placebo was given in the form of vehicle during the anesthesia induction.

Intraoperative outcome(s): Baseline HR and SBP were recorded before induction of anesthesia (mean of 3 values recorded at 1 minute intervals). Post-induction measurements were recorded 30-60 seconds after induction and following intubation every minute for six minutes.

Results(s): A 100 mg dose of esmolol with a low dose (2-3 µg/kg) of fentanyl was effective for blunting the hemodynamic response for tracheal intubation. In the E200 group, the incidence of hypotension was significantly greater than in the E100 or placebo groups.

Oxorn D et al.

Title: Bolus doses of esmolol for the prevention of perioperative hypertension and tachycardia

Journal: Canadian Journal of Anaesthesia

Year: 1990

Purpose of the study: To investigate whether post-intubation hemodynamic perturbations could be prevented of treated with esmolol.

Design: Double-blind RCT

Patients: Forty-eight ASA I-II-classified adult patients undergoing hysterectomy

Intervention: A 20 ml-bolus of solution containing either 100 mg (ESM-100) or 200 mg (ESM-200) of esmolol was injected over 15 seconds before anesthesia induction.

Control: A 20-ml bolus of saline was injected over 15 seconds before anesthesia induction.

Intraoperative outcome(s): Monitoring of the hemodynamic variables continued for at least 15 minutes after administration of the study drug.

Result(s): After induction of anesthesia, the HR and SBP were significantly lower in the ESM-200-group than in the other two groups. Following intubation, the increase in HR was greater in the placebo group compared to other two groups. The BP did not differ between the groups after intubation.

Appendix 4.
Summary of the RCTs reporting intraoperative data on the effect of esmolol in non-cardiac surgery.

Parnass SM et al.

Title: A single bolus dose of esmolol in the prevention of intubation-induced tachycardia and hypertension in an ambulatory surgery unit

Journal: Journal of Clinical Anesthesia

Year: 1990

Purpose of the study: To study the efficacy of esmolol in the prevention of hemodynamic response for endotracheal intubation.

Design: A double-blind RCT

Patients: Thirty adult patients with risk factors for coronary artery disease or tachycardia and hypertension-induced cardiac stress undergoing ambulatory surgery. ASA I patients were excluded.

Intervention: A 20-ml iv-solution of 100 mg or 200 mg of esmolol immediately prior to induction.

Control: A 20-ml iv-solution of placebo immediately prior to induction.

Intraoperative outcome(s): Post-intubation recordings of BP and HR every minute for the first 5 minutes, after that at 10 and 15 minutes.

Result(s): Both esmolol doses effectively blunted the hemodynamic response for intubation.

Singh PP et al.

Title: A comparison of esmolol and labetalol for the treatment of perioperative hypertension in geriatric ambulatory surgical patients

Journal: Canadian Journal of Anaesthesia

Year: 1992

Purpose of the study: To study the efficacy and safety of intravenous esmolol and labetalol for the treatment of perioperative hypertension.

Design: Open RCT

Patients: Twenty-two adult patients undergoing ambulatory cataract surgery under local anesthesia. Their ASA-classification was not reported.

Intervention: Patients with perioperative hypertension (SBP >200 mmHg and/or DBP >100 mmHg measured twice with a 5-minute interval) received intravenous esmolol as an initial bolus of 0.5 mg/kg followed by an infusion of 150-300 µg/kg/min until the end of the operation.

Control: The control group received labetalol as a 5 mg bolus followed by similar doses every 5 minutes as needed (maximum dose 1 mg/kg).

Intraoperative outcome(s): BP and HR were measured with 2-minute intervals during the administration of the study drugs and the performance of the regional anesthesia (retrobulbar block). During the operation and in the recovery room the hemodynamic measurements were made every 15 min.

Result(s): Both intervention and control drugs significantly decreased SBP and DBP within 10 minutes from administration. Esmolol also caused a decrease in HR and the bradycardia was extreme in two patients in the intervention group.

* Fromme GA, et al. Controlled hypotension for orthognathic surgery. Anesth Analg. 1986;56:683-6

Appendix 5.
Data items and completeness score for randomized controlled trials investigating perioperative esmolol medication in adult patients undergoing non-cardiac surgery (max 38 points per 36 data items).

Items	Data completeness score
Patients (P1-P11)	**Max 12**
P1 Multi-center study	2
P2 Number of screened patients	1
P3 Number of eligible patients	1
P4 Number of randomized patients	1
P5 Number of patients with a complete follow-up	1
P6 Type of surgery clearly indicated	1
P7 Pre-existing cardiovascular and/or renal morbidity reported	1
P8 Pre-existing beta blocker treatment reported	1
P9 Pre-existing ECG abnormalities reported	1
Prospective diagnosis of cardiac and renal complications	
P10 Prospective laboratory samples collecting	1
P11 Prospective ECG follow-up	1
Intervention (I1-I4)	**Max 4**
I1 Timing of intervention clearly indicated	1
I2 Type of intervention clearly indicated	1
I3 Dosage of intervention clearly indicated	1
I4 Aberrations from the treatment protocol reported	1
Control group (C1-C5)	**Max 5**
C1 Baseline characteristics – adequate	1
Co-interventions	
C2 Type of co-intervention clearly indicated	1
C3 Timing of co-intervention clearly indicated	1
C4 Dosage of co-intervention clearly indicated	1
C5 Aberrations from the treatment protocol clearly indicated	1
Outcomes (O1-O16)	**Max 17**
O1 30-day survival reported	2
O2 Myocardial infarction	1
O3 Myocardial ischaemia	1

Appendix 5.
Data items and completeness score for randomized controlled trials investigating perioperative esmolol medication in adult patients undergoing non-cardiac surgery (max 38 points per 36 data items).

O4 Cardiac arrest	1
O5 Cardiac death	1
O6 Heart failure	1
O7 Unstable angina pectoris	1
O8 New-onset arrhythmias	1
O9 Composite of cardiac events	1
O10 Acute kidney failure	1
O11 Composite of renal events	1
Adverse effects	
O12 Hypotension	1
O13 Bradycardia	1
O14 Neurologic sequelae	1
O15 Serious infection/sepsis	1
O16 Bronchospasm	1
Total	**Max 38**
Abbreviations: ECG, electrocardiograph.	

Appendix 6.
Characteristics of the primary study patients with and without plasma samples taken.

	All patients N=385 n (%) or median [IQR]	Plasma taken N=275 n (%) or median [IQR]	Plasma not taken N=110 n (%) or median [IQR]	p-value
Age (years)	69 [64–78]	69 [63-77]	71 [64-78]	0.56
Gender (male)	215 (55.8)	159 (57.8)	56 (50.9)	0.26
Comorbidity				
CAD	85 (22.1)	62 (22.5)	23 (20.9)	0.79
Heart failure	44 (11.4)	33 (12.0)	11 (10.0)	0.72
PAD	102 (26.5)	72 (26.2)	30 (27.3)	0.90
Hypertension	232 (60.3)	163 (59.3)	69 (62.7)	0.57
COPD	48 (12.5)	33 (12.0)	15 (13.6)	0.81
DM	107 (27.8)	77(28.0)	30 (27.3)	1.0
Current malignancy	77 (20.0)	57 (20.7)	20 (18.2)	0.77
Prior				
Acute MI	44 (11.4)	32 (11.6)	12 (10.9)	0.72
Coronary revascularisation	51 (13.2)	37 (13.5)	14 (12.7)	1.0
Stroke	85 (15.2)	64 (23.3)	21 (19.1)	0.42
ASA classification				
II	43 (11.2)	32 (11.6)	11 (10.0)	0.72
III	219 (56.9)	161 (58.5)	58 (52.7)	0.31
IV–V	118 (30.6)	79 (28.7)	39 (35.5)	0.22
Preoperative medication				
Statin	199 (51.7)	145 (52.7)	54 (49.1)	0.29
β-blocker	180 (46.8)	128 (46.5)	52 (47.3)	0.91
ACEI/A2RB	198 (51.4)	144 (52.4)	54 (49.1)	0.70
Acetylsalicylic acid	176 (45.7)	127 (46.2)	49 (44.5)	0.82
Clopidogrel	31 (8.1)	25 (9.1)	6 (5.5)	0.50
Gupta score*	0.79 [0.49–2.05]	0.78 [0.49-2.04]	1.17 [0.49-2.48]	0.34
Urgent/emergency operation	221 (57.4)	148 (53.8)	73 (66.4)	0.05

→

Appendix 6.
Characteristics of the primary study patients with and without plasma samples taken.

Preoperative laboratory values				
Hb (g L^{-1})	131 [115–143]	132 [116-143]	128 [114-140]	0.06
Thrombocytes ($\times 10^9$)	238 [193–304]	238 [192-296]	229 [193-311]	0.68
Creatinine (µmol L^{-1})	74 [62–93]	75 [62-94]	75 [62-94]	0.98
TT (%)	92 [73–109]	93 [76-119]	90 [67-107]	0.32
TnT (ng L^{-1})	13 [8–23]	13 [8-23]	13 [9-25]	0.89
Vasopressor load during the day of surgery (mg)	0.48 [0–1.56]	0.69 [0-1.75]	0.2 [0-1.07]	0.02
Nadir Hb during hospitalization (g L^{-1})	105 [89–120]	105 [91-120]	103 [86-116]	0.15

* Gupta PK, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation. 2011;124:381-7.

Abbreviations: IQR, interquartile range; CAD, coronary heart disease; PAD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; MI: myocardial infarction; ASA: American Society of Anesthesiologists; ACEI: angiotensin-converting enzyme inhibitor; A2RB: angiotensin II receptor blocker; Hb: hemoglobin concentration; TT: thromboplastin time; TnT: troponin T

Appendix 7.
Total data completeness scores of the three randomised controlled trials investigating perioperative esmolol intervention in non-cardiac surgery.

	Patients (P1-P9)	**Patients (P10-11)**	**Inter-vention (I1-I4)**	**Control group (C1)**	**Control group (C2-C5)**	**Outcomes (O1-O11)**	**Outcomes (O12-O16)**	**Total score/38**
Raby	7	2	4	1	2	4	0	20
Urban	6	2	4	1	3	3	2	21
Balser	6	1	4	1	4	0	2	18
Mean/ Max	6.3/7	1.7/2	4/4	1/1	3/4	2.3/4	1.3/2	19.7/20